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# *American Journal of* OBSTETRICS AND GYNECOLOGY

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## Gynecology

<i>Abnormal uterine bleeding</i>	Blood dyscrasia as a causative factor in abnormal uterine bleeding <i>H. Melvin Radman, M.D., Baltimore, Maryland</i>	1
	Coagulation studies of patients with abnormal uterine bleeding <i>Arthur J. Seaman, M.D., and Ralph C. Benson, M.D., Portland, Oregon</i>	5
	Postmenopausal uterine bleeding of psychogenic origin <i>Marcel Heiman, M.D., and William J. Shapiro, M.D., New York, New York</i>	11
	Habitual premenstrual spotting following electrocauterization of the cervix: a newly observed phenomenon <i>Louise Branscomb, M.D., Birmingham, Alabama</i>	16
<i>Tumors of the Fallopian tube</i>	Primary carcinoma of the Fallopian tube <i>Glen E. Hayden, M.D., and Edith L. Potter, M.D., Chicago, Illinois</i>	24
	Fibroma of the Fallopian tube <i>Howard M. Seidner, M.D., and J. Robert Thompson, M.D., Chicago, Illinois</i>	32
<i>Gynecological surgery</i>	Surgical treatment of complications resulting from irradiation therapy of cervical cancer <i>Robert E. Dean, M.D., and E. Stewart Taylor, M.D., Denver, Colorado</i>	34
	Extensive myomectomy <i>H. Harold Lardaro, M.D., New York, New York</i>	43

(Contents continued on page 2)

## Contents continued from page 1

	Posterior colpotomy: an avenue for definitive pelvic operations	52
	<i>James H. Smith, Colonel, MC, USA, and John A. Morris, Captain, MC, USA, Denver, Colorado</i>	
	Bloodless technique of cold knife conization (ring biopsy)	62
	<i>Joseph W. Scott, M.D., William B. Welch, M.D., and Thomas F. Blake, M.D., Miami, Florida</i>	
	Construction of a functional vagina	67
	<i>Harold T. Sargis, M.D., Burdett Wylie, M.D., W. S. Thomay, M.D., and Harjiwan Kalani, M.D., Lakewood, Ohio</i>	
	Marsupialization of vulvovaginal (Bartholin) cysts	73
	<i>Philip Jacobson, M.D., Petersburg, Virginia</i>	
Special histology	Basement membranes in the female genital tract	79
	<i>Emmet J. Lamb, M.D., Ivan Fucilla, M.D., and R. R. Greene, M.D., Chicago, Illinois</i>	

## Obstetrics

Physiology of pregnancy	Measurement of uterine blood flow and uterine metabolism. VIII. Uterine and fetal blood flow and oxygen consumption in early human pregnancy	86
	<i>N. S. Assali, M.D., Los Angeles, California, and L. Rauramo, M.D., and T. Peltonen, M.D., Turku, Finland</i>	
	Electrophoretic studies of serum proteins in pregnancy and the puerperium and in newborn infants	99
	<i>George Milles, M.D., Joseph B. Teton, M.D., and Adolph J. Rabinovitz, M.D., Chicago, Illinois</i>	

(Contents continued on page 4)

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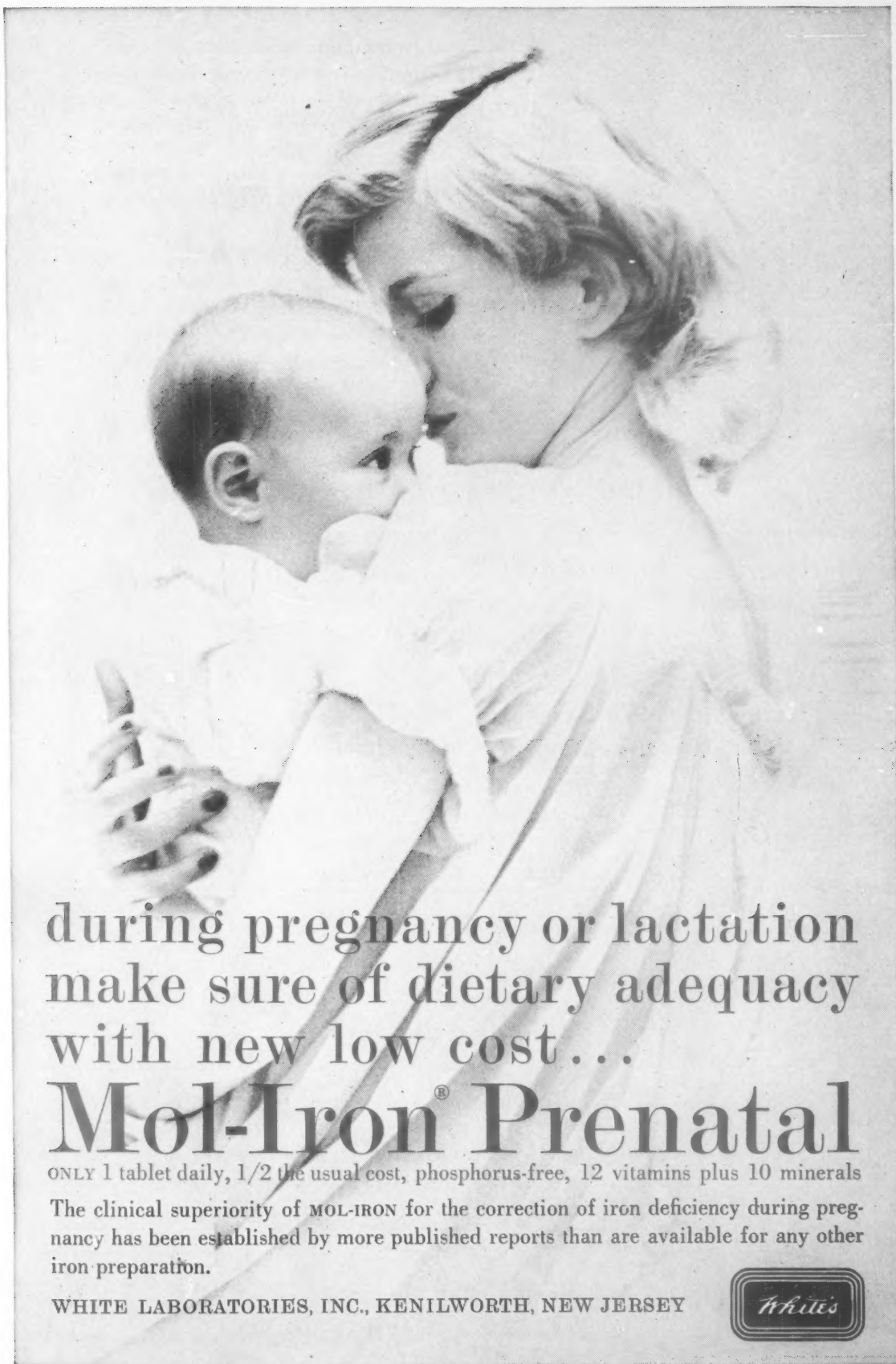
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# Contents continued from page 2

	<b>Lactic dehydrogenase in pregnancy and the puerperium</b>	108
	<i>Dennis P. Heimback, M.D., and Anthony P. Prezyna, M.D., Lackawanna, New York</i>	
	<b>Vitamin B<sub>12</sub> absorption during pregnancy: a controlled study</b>	113
	<i>Richard P. Gotchel, M.D., and B. Frank Lovett, M.D., Camden, New Jersey</i>	
<b>The placenta</b>	<b>Studies in placental permeability</b>	117
	<i>Morrie M. Gelfand, M.D., George J. Streat, M.D., Vitautas Pavilanis, M.D., and Joseph Sternberg, M.D., Montreal, Quebec</i>	
	<b>The significance of placental/fetal weight ratios</b>	134
	<i>William A. Little, M.D., New York, New York</i>	
	<b>A giant placenta</b>	138
	<i>J. Lee Dockery, M.D., Miami, Florida</i>	
<b>Complications of pregnancy</b>	<b>Pregnancy complicated by diabetes</b>	140
	<i>James D. Garnet, M.D., Philadelphia, Pennsylvania</i>	
	<b>Idiopathic thrombocytopenic purpura and pregnancy</b>	148
	<i>M. Leon Tancer, M.D., New York, New York</i>	
	<b>The nephrotic syndrome in pregnancy</b>	154
	<i>H. V. Freidell, M.D., and F. B. Zener, M.D., Santa Barbara, California</i>	
	<b>Intestinal obstruction in pregnancy</b>	157
	<i>Velimir S. Svesko, M.D., and Bernard J. Pisani, M.D., New York, New York</i>	
	<b>Inferior vena cava syndrome in late pregnancy</b>	162
	<i>Bernard E. Cappe, M.D., and Sylvan N. Surks, M.D., New Hyde Park, New York</i>	
	<b>Carcinoma of the cervix and pregnancy</b>	164
	<i>Richard W. Stander, M.D., and John N. Lein, M.D., Indianapolis, Indiana</i>	
	<b>Pseudomonas aeruginosa as a cause of necrotizing renal papillitis</b>	168
	<i>Iwan O. Meyer, M.D., Columbus, Ohio</i>	

(Contents continued on page 6)






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## Contents continued from page 4

---

<i>Labor and delivery</i>	Treatment of threatened premature labor with large doses of progesterone <i>Fritz Fuchs, M.D., and Georg Stakemann, M.D., Copenhagen, Denmark</i>	172
	Hourly variation in onset of labor and rupture of membranes <i>Landrum B. Shettles, M.D., New York, New York</i>	177
	Single application of intravenous Pitocin for induction of labor in toxemias of pregnancy <i>Charles Fields, M.D., and Alexander Varga, M.D., Chicago, Illinois</i>	180

## Department of current opinion

---

<i>Pertinent comments</i>	The relation of nasopharyngeal infection to infertility <i>Bernard Sandler, M.D., D.M.R., D.R.C.O.G., Manchester, England</i>	187
	Mancinism <i>Allan C. Barnes, M.D., Cleveland, Ohio</i>	190

## Editorial

---

The new format	193
----------------	-----

## Reviews and abstracts

---

Books received for review	194
Selected abstracts	195

## Roster

---

Roster of American obstetrical and gynecological societies	204
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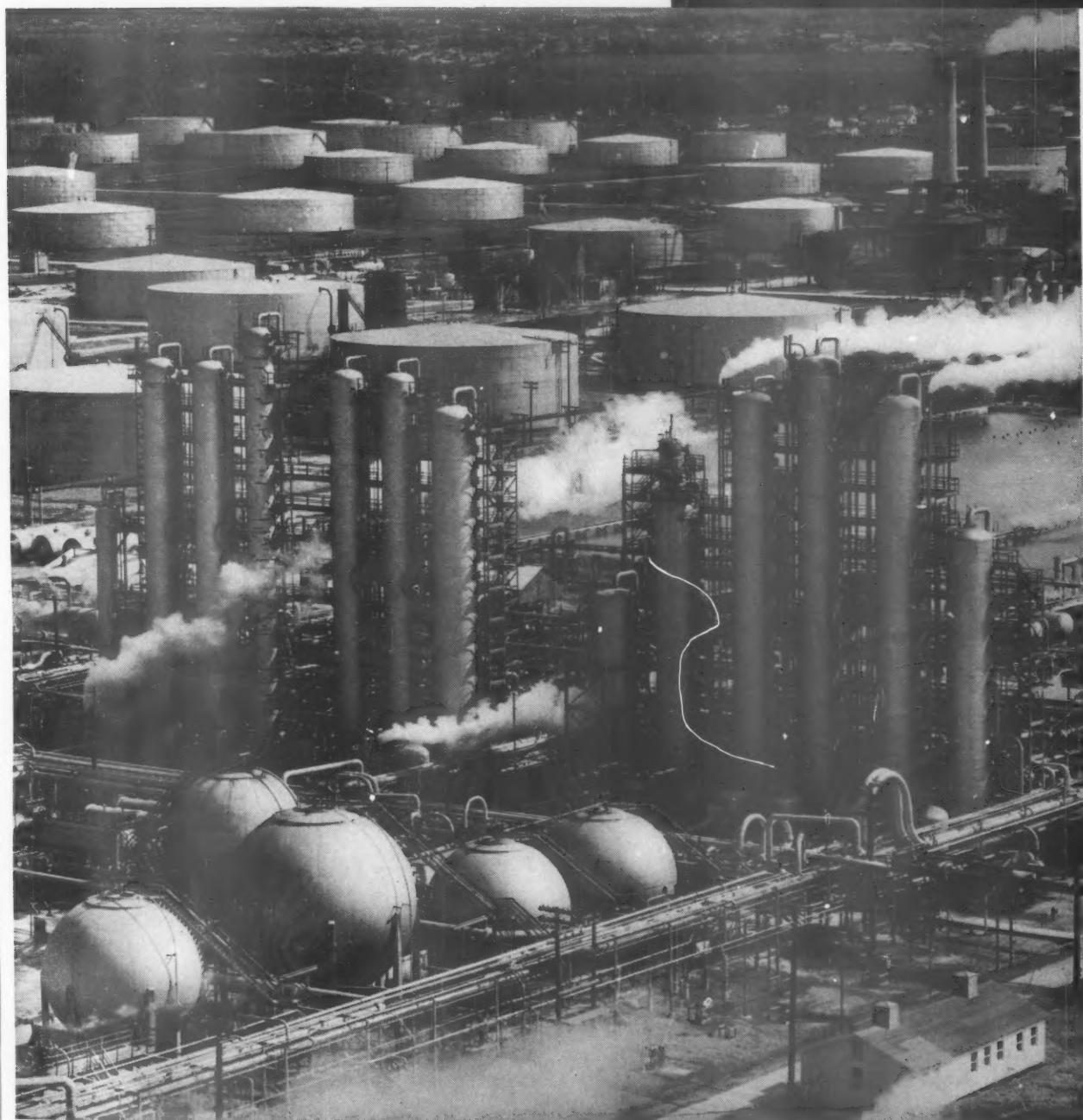
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*Given by intravenous drip, alone or with oxytocin, early in spontaneous or induced labor at term, CERVILAXIN acts physiologically and safely. It (1) softens the cervix, (2) eases delivery, by softening cervical and perineal tissues, and (3) avoids birth injuries, by diminishing cervical and perineal resistance to the expulsive forces of labor. In fact it makes the use of oxytocin safer as well as more efficient.*

CERVILAXIN is supplied in 2-ml. vials containing 20 mg./ml., with detailed instructions for administration by intravenous drip.

References: 1. Rothman, E., Bentley, W.G., and Floyd, W.S.: Am. J. Obst. & Gynec. 78:38, 1959. 2. Stone, M.L., Sedlis, A., and Zuckerman, M.: *ibid.* 76:544, 1958. 3. Sands, R.X.: Canad. M.A.J. 78:935, 1958.

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"'Just a little case of cystitis' may actually have already involved the kidney parenchyma before the bladder became infected.'"<sup>1</sup>

"The first evidence of inflammatory disease of kidney or prostate often is vesical irritability."<sup>2</sup>



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brand of nitrofurantoin

for rapid control of infection throughout the G. U. system

Rapid bactericidal action against a wide range of gram-positive and gram-negative bacteria including organisms such as staphylococci, Proteus and certain strains of Pseudomonas, resistant to other agents

- actively excreted by the tubule cells in addition to glomerular filtration
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- excellent tolerance—nontoxic to kidneys, liver and blood-forming organs
- safe for long-term administration

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REFERENCES: 1. Editorial: J.M.A. Georgia 46:433, 1957. 2. Colby, F. H.: Essential Urology, Baltimore, The Williams & Wilkins Co., 1953, p. 330.

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in every type of surgery

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the physiologic hemostat

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1. Johnson, J. F.: Paper presented at Symposium on Blood, Wayne State University, Detroit, Michigan, Jan. 18, 1957; cited in *M. Science* 1:33 (Mar. 25) 1957; *Proc. Soc. Exper. Biol. & Med.* 94:92 (Jan.) 1957. 2. Published and unpublished case reports, Ayerst Laboratories. 3. Rigg, J. P.: *Digest Ophth. & Otolaryng.* 20:28 (Nov.) 1957. 4. Rigual, R.: *Ibid.*, p. 3. 5. Servoss, H. M., and Shapiro, F.: *Ibid.*, p. 10. 6. Menger, H. C.: *J.A.M.A.* 159:546 (Oct. 8) 1955.

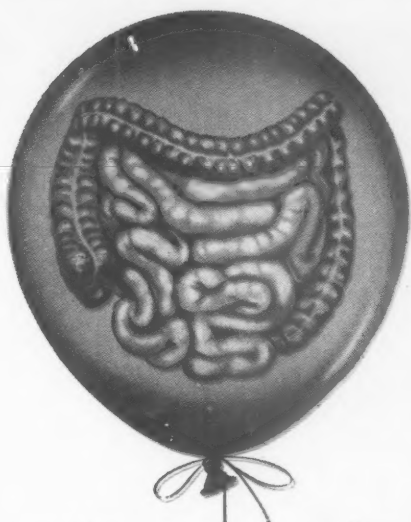


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can be prevented...*

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***A Routine Procedure for the Early  
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Intestinal Activity***

- effectively prevents and corrects abdominal distention . . . and retention of flatus and feces
- restores normal peristaltic activity, physiologically

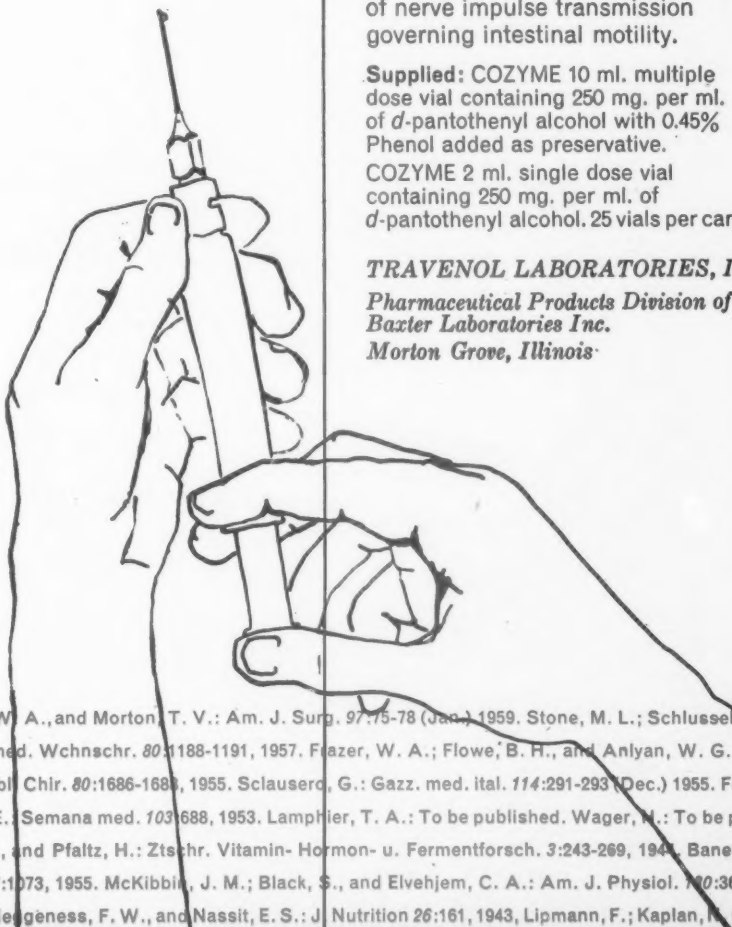
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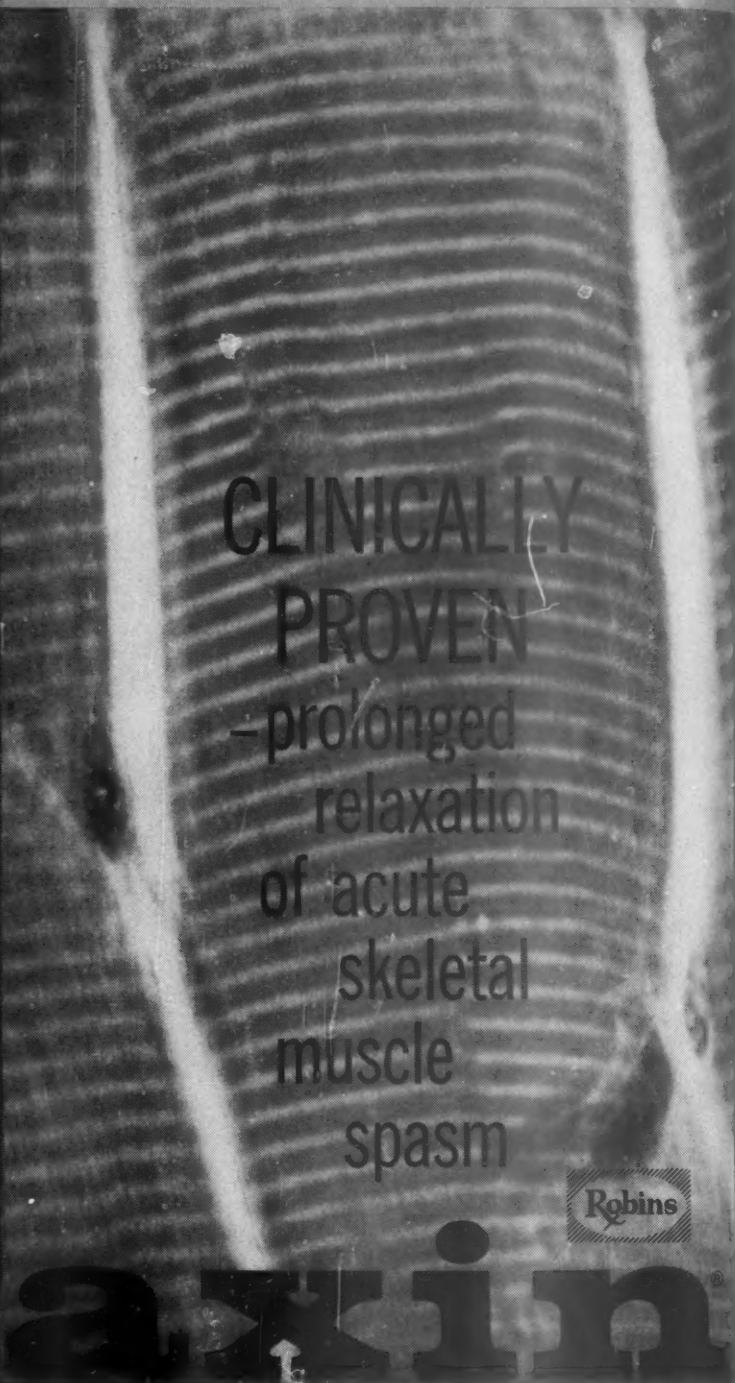
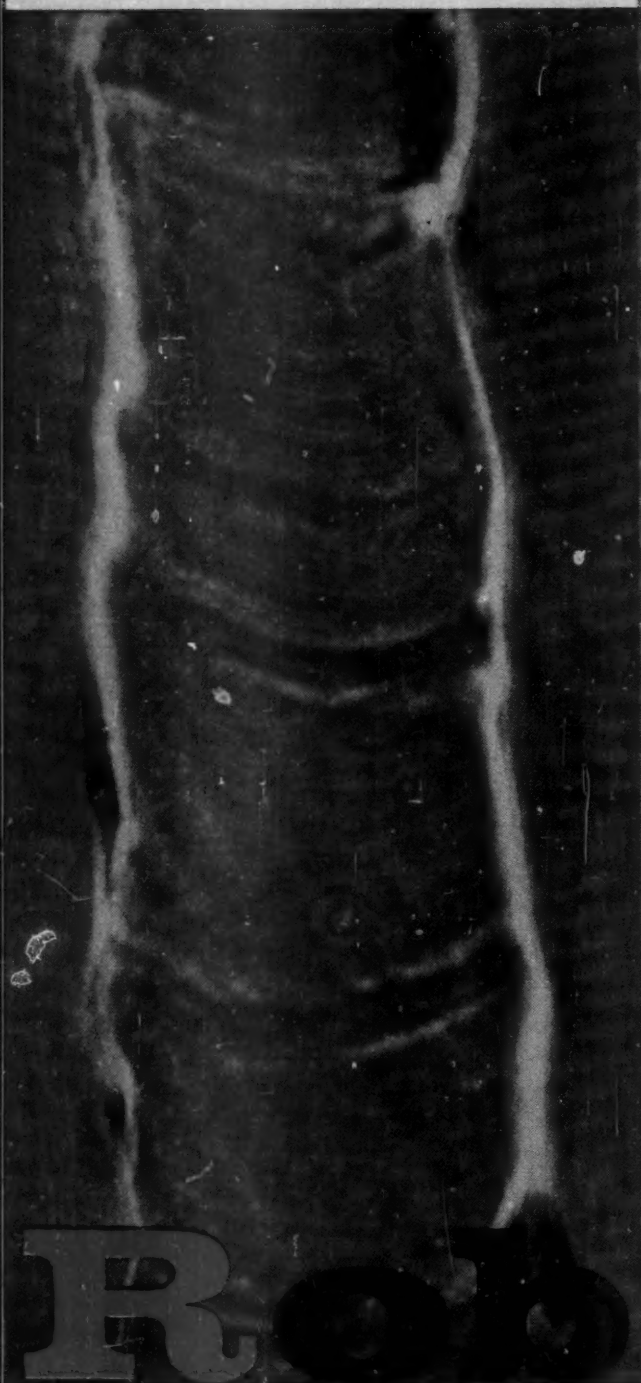


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Fiber of skeletal muscle in spasm

Fiber of skeletal muscle relaxed (photomicrographs)



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TABLETS

Summary of six published clinical studies:

**ROBAXIN BENEFICIAL IN 92.4% OF SKELETAL MUSCLE SPASM CASES**

	NO. PATIENTS	RESPONSE			
		"marked"	moderate	slight	none
Carpenter <sup>1</sup>	33	26	6	1	—
Forsyth <sup>2</sup>	58	37	20	—	1
Lewis <sup>3</sup>	38	25	6	—	7
O'Doherty & Shields <sup>4</sup>	17	14	2	1	0
Park <sup>5</sup>	30	27	—	2	1
Plumb <sup>6</sup>	60	55	—	—	5
<b>TOTALS</b>	<b>236</b>	<b>184</b> <b>(78.0%)</b>	<b>34</b> <b>(14.4%)</b>	<b>4</b>	<b>14</b>

• **Highly potent—and long acting.**<sup>1,2,3</sup>

• **Relatively free of adverse side effects.**<sup>1,2,3,5,6</sup>

• **In ordinary dosage, does not reduce muscle strength or reflex activity.**<sup>1</sup>

**REFERENCES:** 1. Carpenter, E. B.: Southern M. J. 51:627, 1958. 2. Forsyth, H. F.: J.A.M.A. 167:163, 1958. 3. Lewis, W. B.: California Med. 90:26, 1959. 4. O'Doherty, D. S., and Shields, C. D.: J.A.M.A. 167:160, 1958. 5. Park, H. W.: J.A.M.A. 167:168, 1958. 6. Plumb, C. S.: Journal-Lancet 78:531, 1958.

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DEMEROL (BRAND OF MEPERIDINE), TRADEMARK REG. U.S. PAT. OFF.

*Winthrop*

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NEW YORK 18, N. Y.

90% of anxious, agitated  
*and* apathetic office patients  
calmed *without* drowsiness  
and with normal drive restored...  
*on one or two 0.25 mg. tablets b.i.d.:*

This is the pattern of performance for

**PERMITIL<sup>®</sup>**

Fluphenazine dihydrochloride

## *In Anxiety and Anxiety-induced Depression*

"In contrast to other phenothiazines, it [PERMITIL] mitigates apathy, indifference, inertia and anxiety-induced fatigue. Thus, instead of impeding effective performance of daily tasks, it increases efficiency by facilitating psychic relaxation. Consequently, acceptance of this drug, especially by office patients, has been excellent."<sup>1</sup>

- In 608 patients with anxiety and anxiety-induced fatigue or depression, PERMITIL, administered in small daily doses of 0.5 mg. to 1 mg., produced significant improvement in 90%.<sup>2</sup>
- PERMITIL is virtually free from side effects at recommended dosage levels.
- Patients become calm without being drowsy and normal drive is restored.
- Onset of action is rapid; effect is prolonged.
- PERMITIL does not potentiate barbiturates or non-barbiturate sedatives and can be used with impunity with such agents.

**How to prescribe PERMITIL:** The lowest dose of PERMITIL that will produce the desired clinical effect should be used. The recommended dose for most adults is one 0.25 mg. tablet twice a day (taken morning and afternoon). Increase to two 0.25 mg. tablets twice a day if required. Total daily dosage in excess of 1 mg. should be employed only in patients with relatively severe symptoms which are uncontrolled at lower dosage. In such patients, the total daily dose may be increased to a maximum of 2 mg., given in divided amounts. Complete information concerning the use of PERMITIL is available on request.

**SUPPLIED:** Tablets, 0.25 mg., bottles of 50 and 500.

**REFERENCES:** 1. Ayd, F. J., Jr.: *Current Therapeutic Research* 1:41 (Oct.) 1959.  
2. Recent compilation of case reports received by the Medical Department, White Laboratories, Inc.



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*White*

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**IN NAUSEA AND VOMITING  
OF PREGNANCY**





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## SPECIFIC

Avoids unnecessarily  
diffuse or diverse  
drug action; effective  
in economical  
once-a-day dosage

## ESTABLISHED

6-year record of suc-  
cessful use in daily  
practice; consistently  
favorable reports<sup>1-10</sup>

## UNCOMPLICATED

Has no known contraindi-  
cations; free of hepatic,  
hypotensive, and hemato-  
logic hazards observed  
with phenothiazines

# BONINE\*

Trade name of meprobamate hydrochloride  
**FORMERLY BONAMINE**

### SUPPLIED:

BONINE Tablets, scored, 25 mg.

BONINE Chewing Tablets,  
mint-flavored, 25 mg.

BONINE Elixir, cherry-flavored, ideal for  
children, 12.5 mg. per teaspoonful (5 cc.).

**DOSEAGE:** Adults, 25 to 50 mg. each day.  
Children, usually half the adult dose.

### BONINE REFERENCES:

1. Moyer, J. H. *M. Clin. Pharmacol.* 1957, p. 463.
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10. *J. Clin. Pharm.*, et al., *J. Clin. Pharm.*

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superior product

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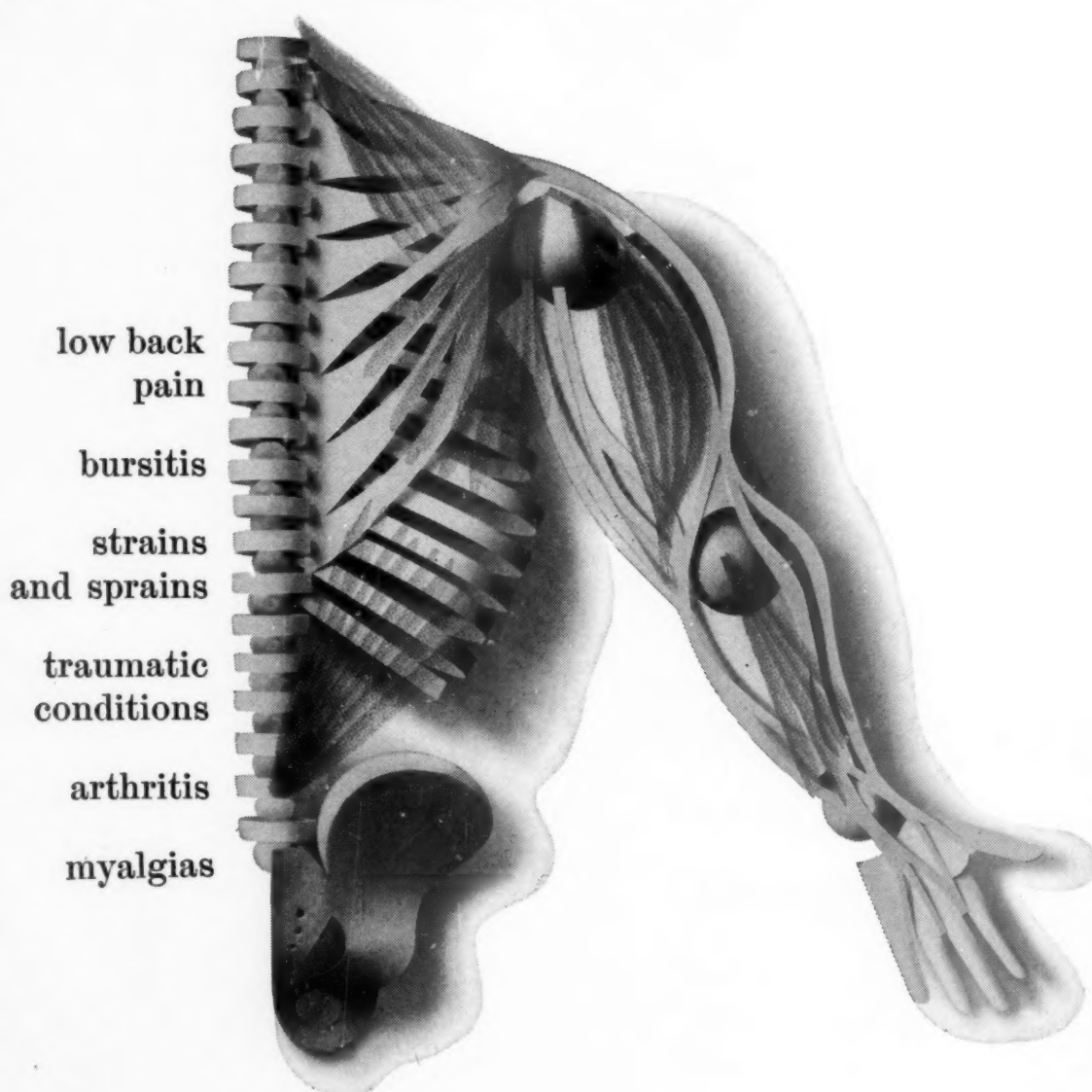
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- potent...fast relief in acute conditions
- safe...even for prolonged use in chronic cases



**SOMA RELIEVES PAIN** in a unique way by modifying central perception of pain without abolishing natural defense reflexes.

**SOMA RELAXES MUSCLE SPASM** ... approximately 8 times more potent than meprobamate or mephenesin.

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Wein, A.B.: The Use of Carisoprodol in Orthopedic Surgery and Rehabilitation. Proceedings of the Symposium on the Pharmacology and Clinical Usefulness of Carisoprodol. Wayne State University Press, Detroit, 1959, p. 156.

In a double-blind study, SOMA was reported to be "clinically effective to a highly significant degree." (92 patients.) Cooper, C. D., and Epstein, J. H.: The Clinical Evaluation of Carisoprodol by a double-blind technique. *Ibid.* p. 97.

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*Notable safety*—extremely low toxicity; no known contraindications; side effects are rare; drowsiness may occur, usually at higher dosage

*Fast action*—starts to act promptly

*Sustained effect*—relief lasts up to 6 hours

*Easy to use*—usual adult dose is one 350 mg. tablet 3 times daily and at bedtime

*Supplied*—as white, coated 350 mg. tablets, bottles of 50.

Also available for pediatric use: 250 mg. orange capsules, bottles of 50.

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(carisoprodol Wallace)

The only drug combining analgesia with muscle relaxation in a single molecule

**BIBLIOGRAPHY:** 1. Berger, F. M., Kletskin, M., Ludwig, B. J., Margolin, S. and Powell, L. S.: J. Pharm. Exp. Ther. 127:66, (Sept.) 1959. 2. Leake, Chauncey D.: Proceedings of the Symposium on The Pharmacology and Clinical Usefulness of Carisoprodol, Wayne State University Press, Detroit, 1959, p. 8. 3. Kestler, Otto: *Ibid.* p. 143. 4. Proctor, Richard C.: *Ibid.* p. 122. 5. Berger, Frank M.: *Ibid.* p. 25. 6. Goodgold, Joseph, Hohmann, Thomas and Tajima, Toshihiro: *Ibid.* p. 66. 7. Gammon, George D. and Tucker, Samuel: *Ibid.* p. 70. 8. Baird, Henry W. and Menta, Dominic A.: *Ibid.* p. 85. 9. Cooper, C. David and Epstein, Jerome H.: *Ibid.* p. 97. 10. Korst, Donald R., Gerard, R. W., Miller, James G., Small, Iver F., Graham, I. J. and Winkelman, Eugene I.: *Ibid.* p. 104. 11. Friedman, Arnold P.: *Ibid.* p. 115. 12. Trimpi, Howard D.: *Ibid.* p. 150. 13. Wein, Arthur B.: *Ibid.* p. 156. 14. Olds, James and Travis, R. P.: *Ibid.* p. 39. 15. Hess, Eckhard H., Polt, James M. and Goodwin, Elizabeth: *Ibid.* p. 51. 16. Phelps, Winthrop M.: *Ibid.* p. 131. 17. Spears, Catherine E.: *Ibid.* p. 138. 18. Hyde, L. P. and Hough, Charles E.: *Ibid.* p. 166. 19. Spears, Catherine E. and Phelps, Winthrop M.: Arch. Pediat., 76:287 (July) 1959. 20. Phelps, Winthrop M.: Arch. Pediat., 76:243, (June) 1959. 21. Friedman, Arnold P.: Paper presented at Scientific Meeting, New York State Society of Industrial Medicine, Inc., New York, Sept. 30, 1959. 22. Frankel, Kalman: *Ibid.* 23. Fransway, Robert L.: *Ibid.* 24. Kuge, T.: Unpublished reports.

Literature and samples on request.



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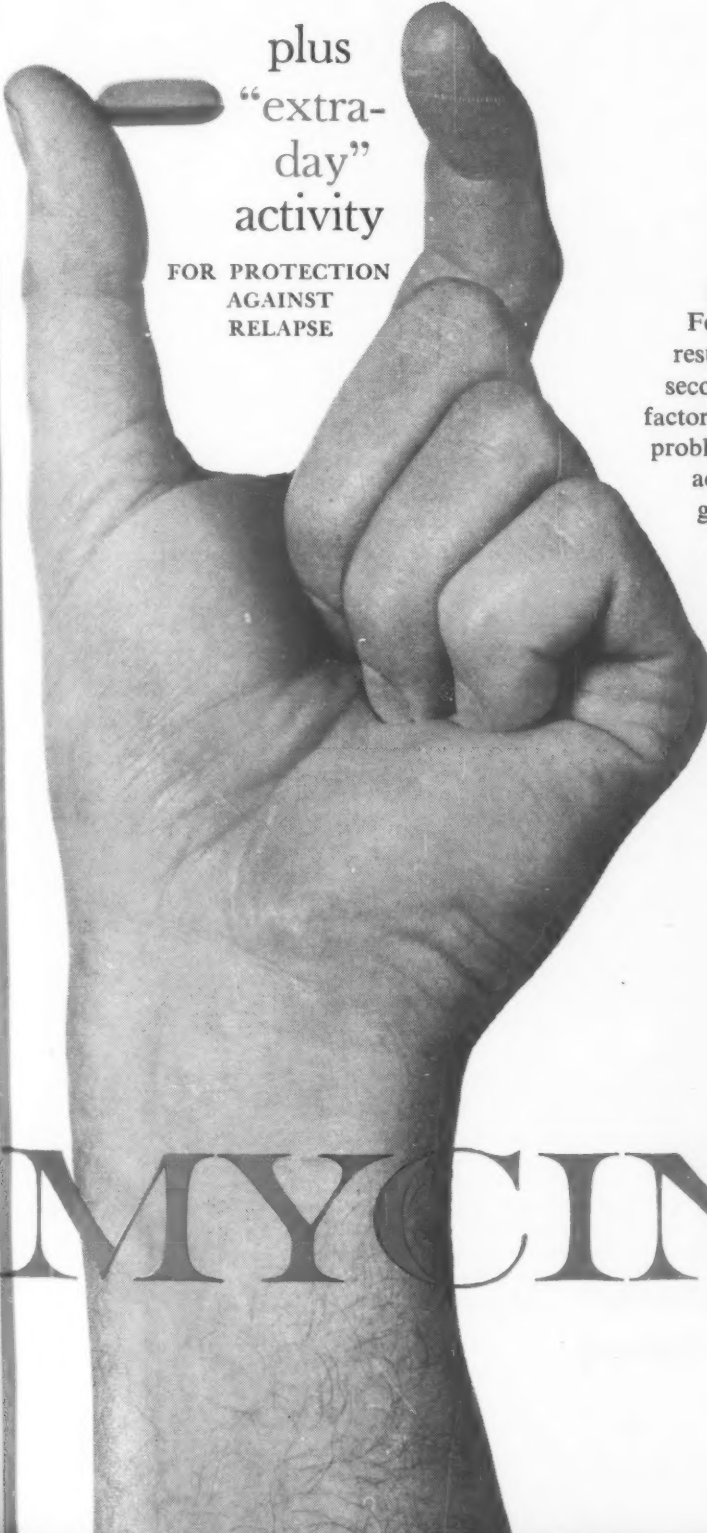
\*Hirsch, H. A., and Finland, M.:  
*New England J. Med.*  
260:1099 (May 28) 1959.

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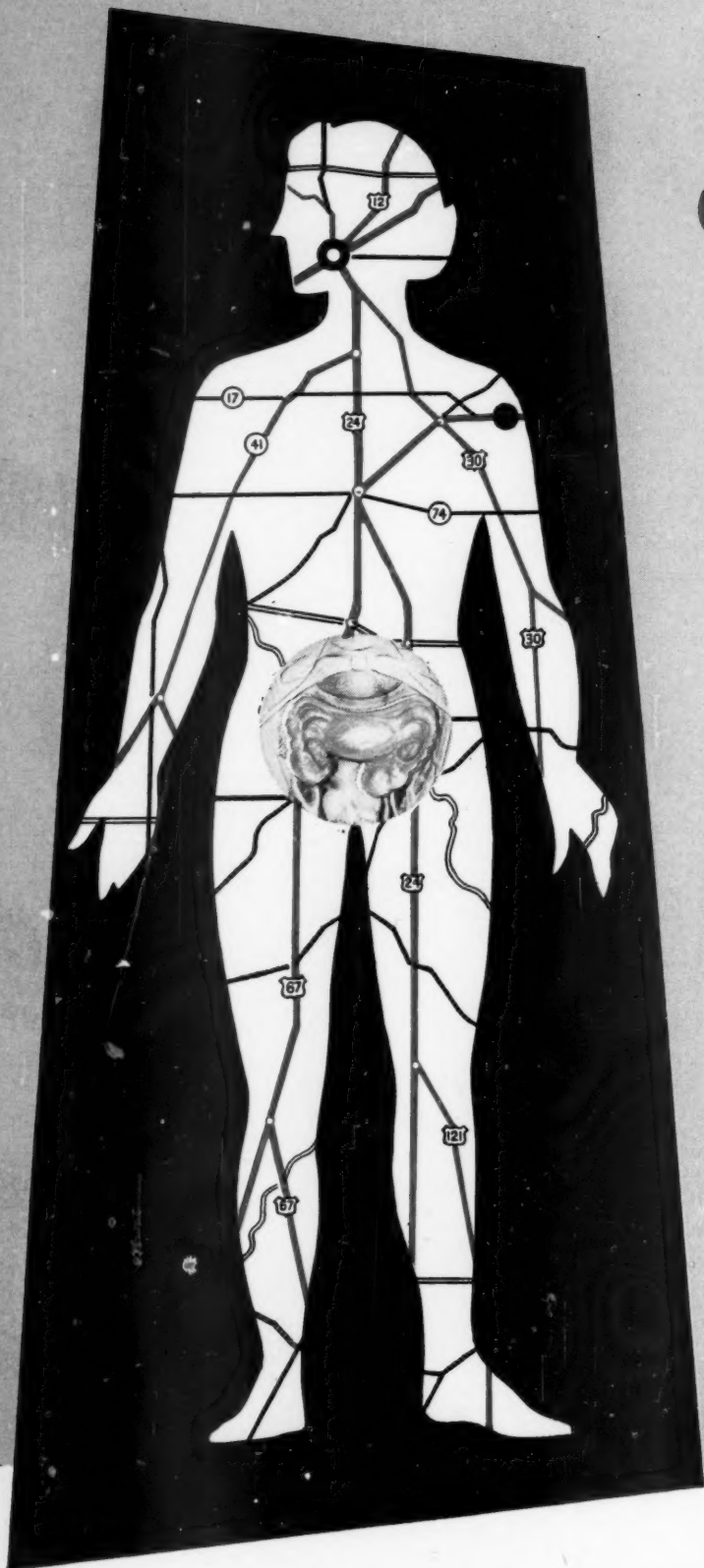
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# Naturētin

Squibb Benzydrolumethiazide

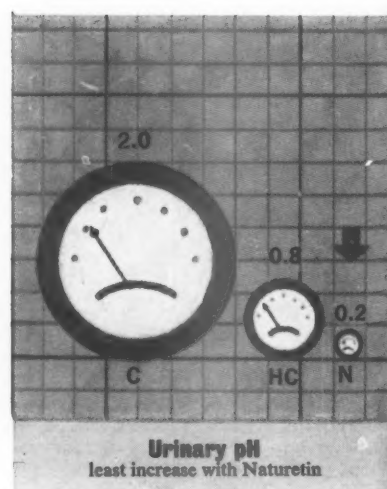
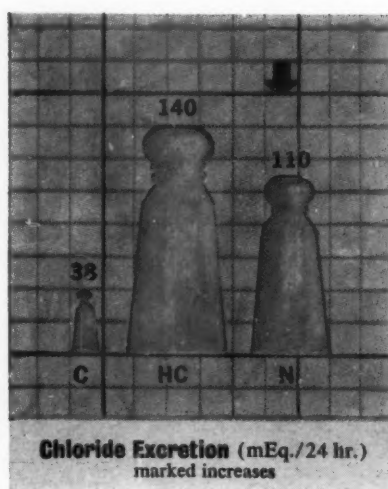
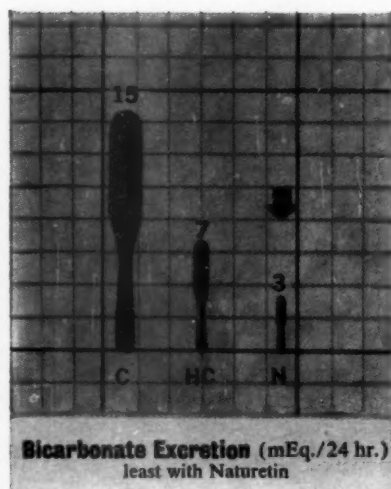
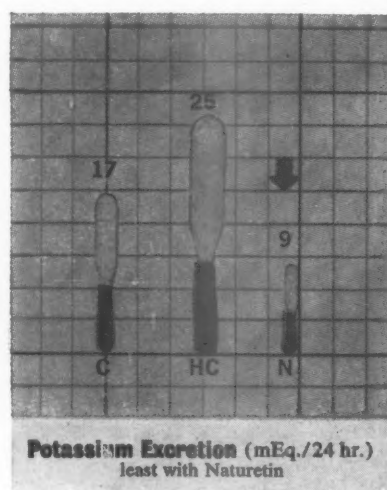
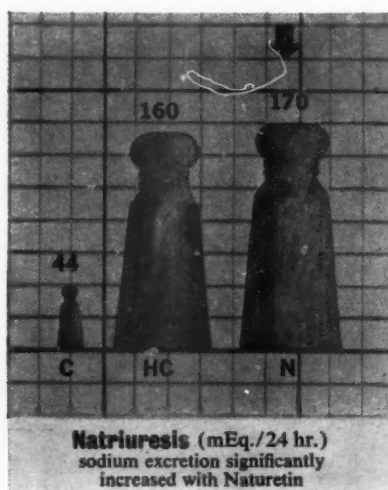
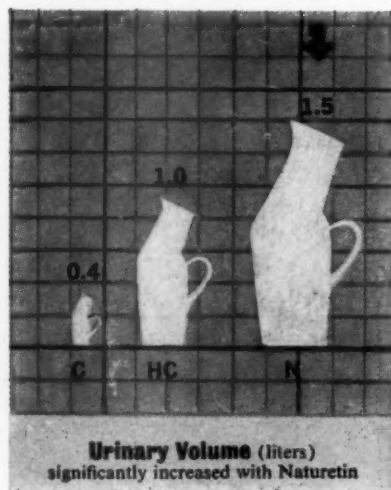


# Naturetin

Squibb Benzhydroflumethiazide

more closely approaches the ideal diuretic

Comparison of electrolyte excretion pattern for the 24 hours following typical doses of chlorothiazide, hydrochlorothiazide, and Naturetin<sup>1</sup>



Typical Doses: Chlorothiazide—1,000 mg.; Hydrochlorothiazide—50 mg.; Naturetin (Benzhydroflumethiazide)—5 mg.

1. Adapted from: Ford, R. V., Squibb Clin. Res. Notes 2:1 (Dec.) 1959.



## a single 5 mg. tablet once a day provides all these advantages<sup>2</sup>

- prolonged action — in excess of 18 hours
- convenient once-a-day dosage
- low daily dosage — more economical for the patient
- no significant alteration in normal electrolyte excretion pattern
- repetitively effective as a diuretic and antihypertensive
- greater potency mg. for mg.—more than 100 times as potent as chlorothiazide
- potency maintained with continued administration
- low toxicity — few side effects — low salt diets not necessary
- comparative studies with chlorothiazide, hydrochlorothiazide, and Naturetin disclose that smallest doses of Naturetin produce greater weight loss per day
- in hypertension, Naturetin, alone or in combination with other anti-hypertensives, produces significant decreases in mean blood pressure and other favorable clinical effects
- purpura and agranulocytosis not observed
- allergic reactions rarely observed

<sup>2</sup>Reports (1959) to the Squibb Institute for Medical Research.

**Naturetin**—*Indications*: in control of edema when diuresis is required, in congestive heart failure, in the premenstrual syndrome, nephrosis and nephritis, cirrhosis with ascites, edema induced by drugs (certain steroids); in the management of hypertension, used alone, combined with Raudixin (Squibb Rauwolfia Serpentina Whole Root), or with other antihypertensive drugs, such as ganglionic blocking agents.

*Contraindications*: none, except in complete renal shutdown.

*Precautions*: when Naturetin is added to an antihypertensive regimen including hydralazine, veratrum, and/or ganglionic blocking agents, immediate reduction must be made in the dosage for all preparations; the dosage for ganglionic blocking agents must be decreased by 50% to avoid a precipitous drop in blood pressure. This also applies if these hypotensive drugs are added to an established Naturetin regimen . . . in hypochloremic alkalosis with or without hypokalemia . . . in cirrhotic patients or those on digitalis therapy when reductions in serum potassium are noted . . . in diabetic patients or those predisposed to diabetes . . . when increased uric acid concentrations are noted . . . when signs—leg or abdominal cramps, pruritus, paresthesia, rash—suggestive of hypersensitivity, are noted.

**Naturetin**—*Dosage*: in edema, average dose, 5 mg., once daily, preferably in the morning; to initiate therapy, up to 20 mg., once daily in divided doses; for maintenance, 2.5 to 5.0 mg., daily in a single dose. *In hypertension*: suggested initial dose, 5 to 20 mg. daily; for maintenance, 2.5 to 15 mg. daily, depending on the individual response of the patient. When Naturetin is added to an anti-hypertensive regimen with other agents, lower maintenance doses of each drug should be used.

**Naturetin**—*Supplied*: tablets of 2.5 mg. and 5 mg. (scored).

\*RAUDIXIN® AND \*NATURETIN® ARE SQUIBB TRADEMARKS.

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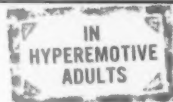
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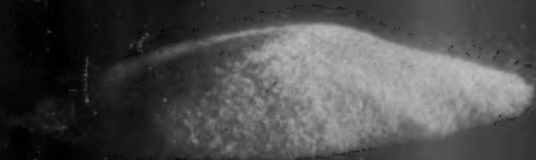
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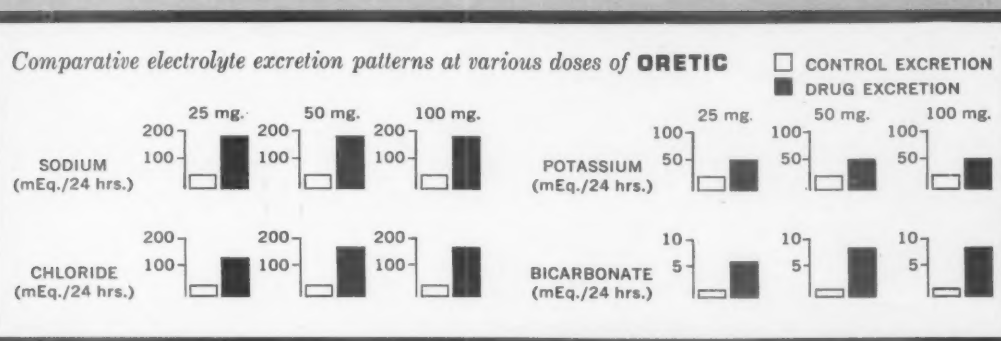
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#### **References:**

1. Reports on file, Roche Laboratories.
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Krantz, J. C., Jr.: The restless patient — A psychologic and pharmacologic viewpoint.  
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Ensey, J. E.: Am. J. Obst. 77:155, 1959

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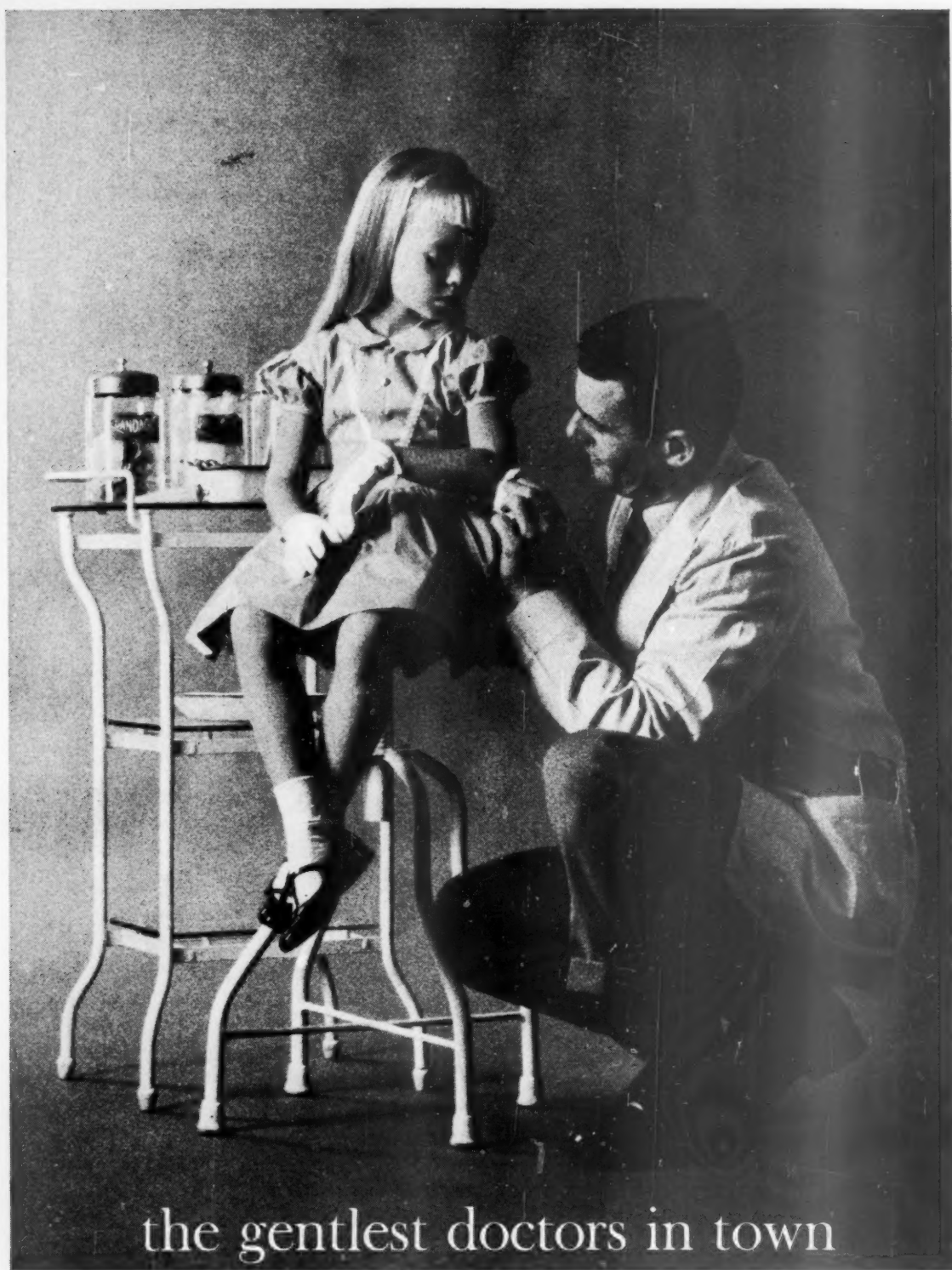
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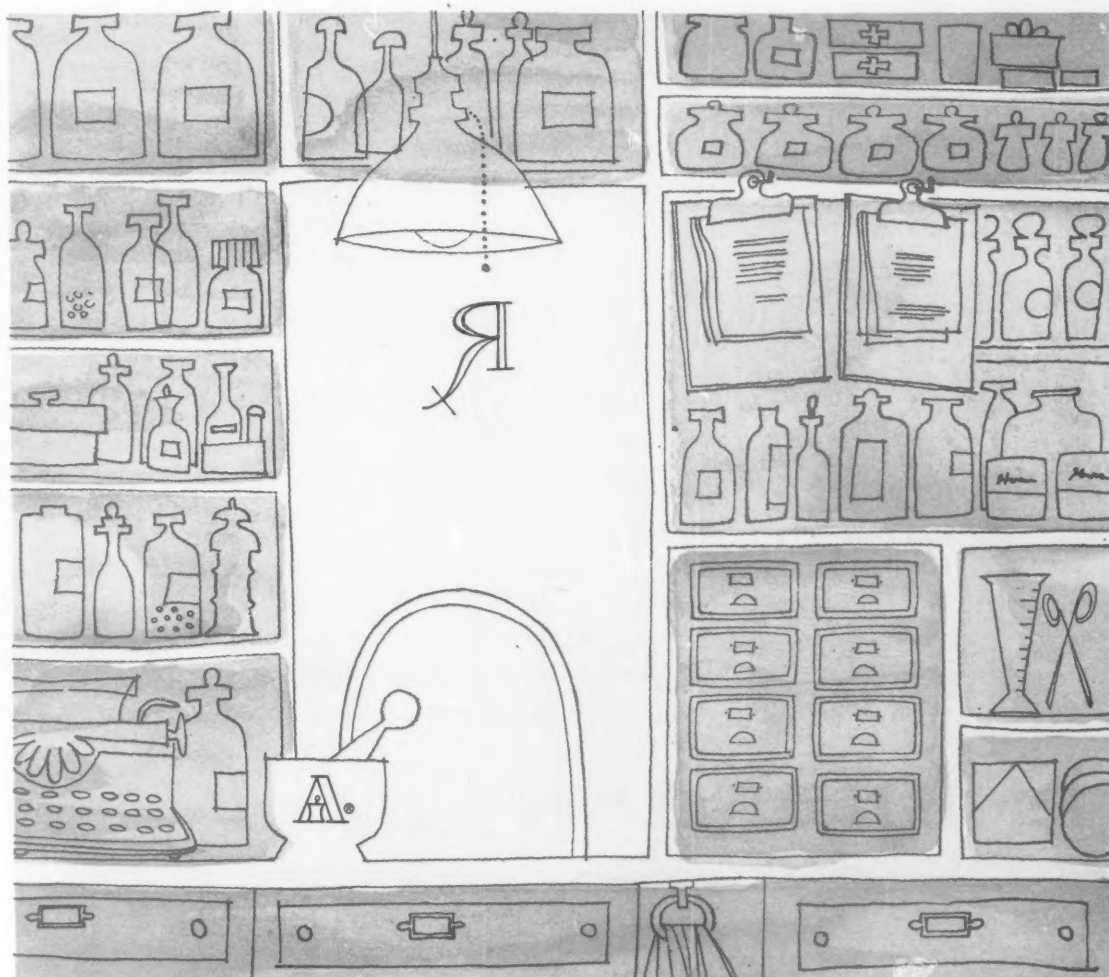
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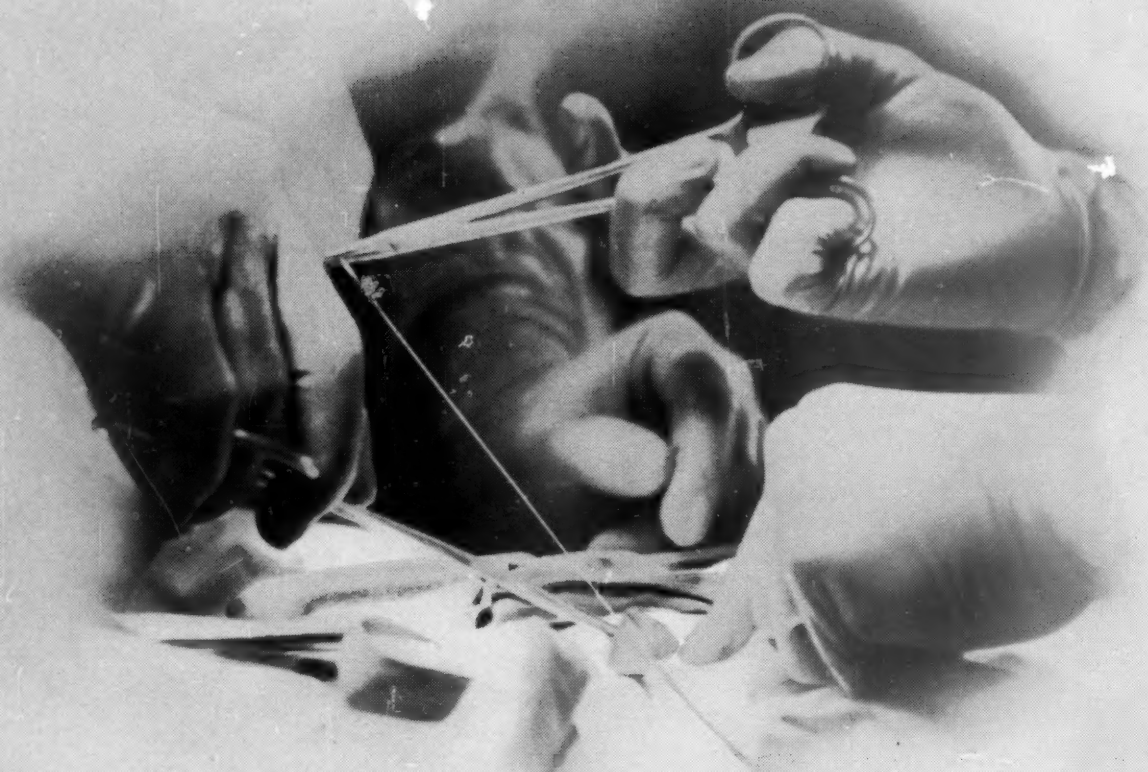


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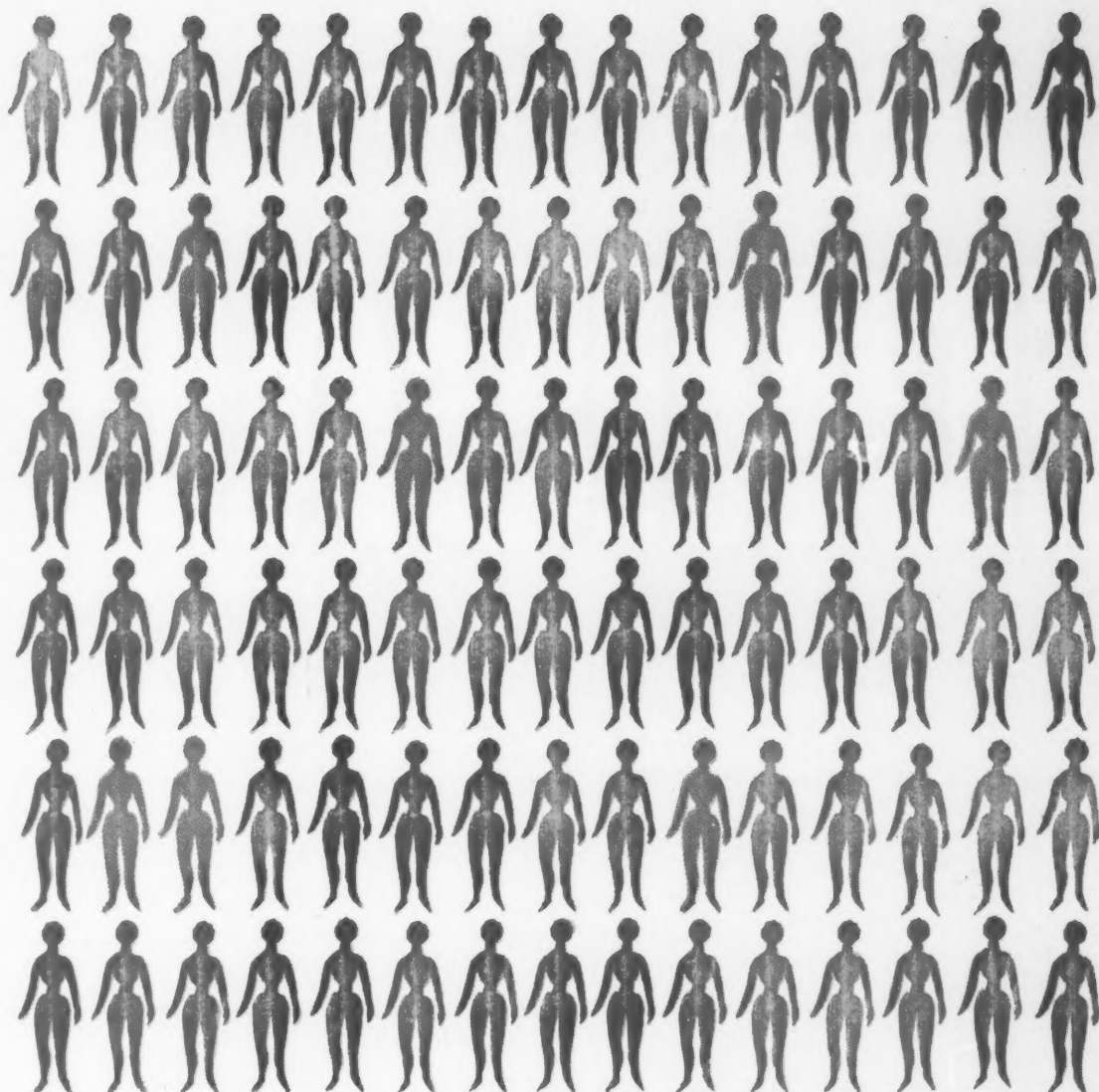
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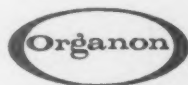




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With the addition of Nugestoral to their anti-abortion regimen, Murphy *et al.*\* brought 78 of 86 habitual aborters to full-term. Nugestoral helps by providing in each daily dose of three tablets 45.0 mg. Progestoral® (ethisterone), 525.0 mg. vitamin C, 487.5 mg. purified hesperidin, 6.0 mg. vitamin K, 10.5 mg. vitamin E. Boxes of 30 and 100.

**NUGESTORAL®**



Organon Inc.  
Orange, New Jersey

\*Murphy, H. S., et al., Scientific Exhibit, A.M.A., Dec. 1-4, 1959, Dallas, Texas.

*To quickly relieve the cramps and pain, to ease  
the headache, to chase the "blues" away*

**in DYSMENORRHEA**

*prescribe what is virtually specific*

# EDRISAL®

*2 tablets every 3 hours*

- *Antispasmodic*
- *Analgesic*
- *Antidepressant*



and when the pain is extremely severe,  
there is also available  
"EDRISAL with CODEINE" (1 gr. & ½ gr.)

SMITH  
KLINE &  
FRENCH



The great operatic works of Rossini have been enjoyed by millions for many decades

## THINGS THAT ENDURE

Good things endure... a work of art, a literary classic, a proud bridge... a dependable pharmaceutical. Such is **Desitin Ointment**. For over 35 years Desitin Ointment has endured as an incomparable, safe way to prevent and clear up diaper rash... and as a soothing, healing application in wounds, burns, external ulcers and other skin injuries.

Desitin®

DESITIN CHEMICAL COMPANY PROVIDENCE 4, R. I.





*before, during, and after childbirth*

**VISTARIL®**...eases mental and physical discomfort

hydroxyzine pamoate

When you give her VISTARIL, confidence replaces anxiety—but not to the point of euphoria. The effectiveness of VISTARIL in pre- and postpartum nausea and vomiting adds greatly to the patient's comfort. VISTARIL enhances the action of opiates, thus decreasing narcotic requirements and lessening the possibility of respiratory depression and reduced circulatory and cortical function.

*Supply:* Capsules, 25 mg., 50 mg. and 100 mg.; Oral Suspension, 25 mg. per 5 cc. teaspoonful; Parenteral Solution, 10 cc. vials and 2 cc. Steraject® Cartridges—25 mg. hydroxyzine HCl per cc.

*A Professional Information Booklet containing further information is available from the Medical Department on request.*

**Pfizer** Science for the world's well-being™

PFIZER LABORATORIES, Div., Chas. Pfizer & Co., Inc., Brooklyn 6, N. Y.



**all through pregnancy ...  
a cheerful outlook  
without autonomic toxicity reactions**



By permission of the Cleveland Health Museum, possessors of the original

relieves  
anxiety  
insomnia  
fretfulness  
tension  
headache  
muscular  
tension

One of your safest adjuncts for  
successful management of pregnancy

**Equanil**  
Meprobamate, Wyeth  
Philadelphia 1, Pa.

in one preparation  
the answer to your  
three most important  
requirements in  
a douche

**For a dependable and  
effective means of treating  
non-specific leukorrhea**

**For adjunctive therapy in  
*Trichomonas Vaginalis* vaginitis and  
other specific infections**

**For personal cleanliness  
and the prevention of  
irritation and inflammation**



TRICHOTINE is the first major douche to contain sodium lauryl sulfate, a detergent of the highest order of efficiency. TRICHOTINE penetrates and dissolves the viscid film covering the vaginal mucosa; gets down in the rugal folds, carrying medication directly to the mucosa and the invading organisms.

TRICHOTINE is a potent bactericide and fungicide, penetrating the walls

---

**TRICHOTINE<sup>®</sup>**



of many micro-organisms. "The douche solution is an effective agent against *Trichomonas Vaginalis*, *Monilia Albicans*, anaerobic organisms including a potent strain of streptococci that sometimes cause severe infections, and other non-specific vaginal micro-organisms."<sup>1</sup>

TRICHOTINE actually favors epithelial growth and healing, and the relief it affords from pruritis is quite striking.

For personal cleanliness, especially as a post-coital and post-menstrual douche, TRICHOTINE is designed to meet all the requirements of feminine hygiene. As an effective cleanser for office use, or for treatment, or for routine home douching, TRICHOTINE will prove satisfactory to you and its soothing, refreshing action will be reassuring to your patients.<sup>1</sup> Karnaky, K.J.: *Med. Record and Annals*, Houston 46:296 (Nov. 1952).

*The Fesler Company, Inc., 375 Fairfield Avenue, Stamford, Conn.*

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**TRICHOTINE®**

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**TRICHOTINE®**



**in edema of pregnancy**

**"gratifying relief..."**

**in all patients**

**treated with**

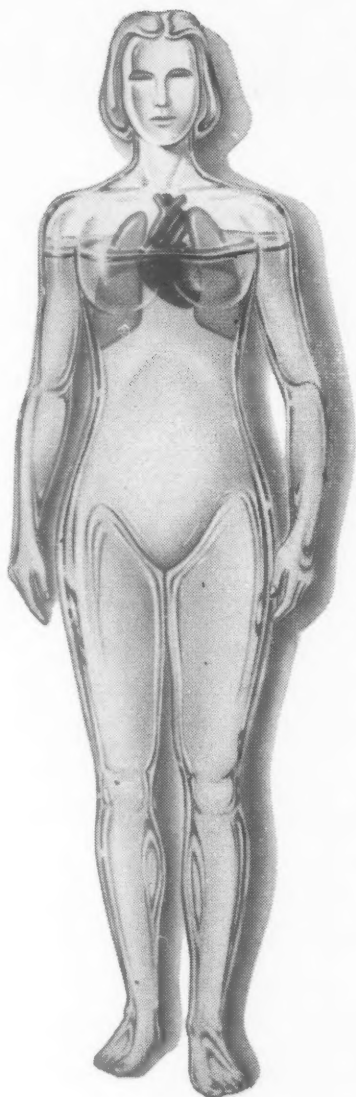


**HYDRODIURIL<sup>®</sup>**

HYDROCHLOROTHIAZIDE

**increased potency—without corresponding increase in side effects**

Ford, Ralph V.: *Southern Med. J.* 52: 40, (Jan.) 1959



“Hydrochlorothiazide was given to patients with edema (mild to moderate) of varied etiology...”

“There were...5 women in the third trimester of pregnancy.” In these patients the cumulative weight loss was 2 pounds after seven days of therapy and 4 pounds after twenty-one days. Gratifying relief of edema was observed in all patients.

**DOSAGE:** One or two 50 mg. tablets HYDRODIURIL once or twice a day, depending upon the condition and individual patient response.

**SUPPLIED:** 25 mg. and 50 mg. scored tablets HYDRODIURIL (Hydrochlorothiazide) in bottles of 100 and 1,000.

HYDRODIURIL is a trademark of Merck & Co., INC.

Additional information on HYDRODIURIL is available to the physician on request.

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**MERCK SHARP & DOHME**  
Division of Merck & Co., INC. Philadelphia 1, Pa.



## SYMPOSIUM REPORT:

### ALTAFUR in antibiotic-resistant staphylococcal infections

ALTAFUR proved superior to any other single agent against staphylococcal infections encountered in the pediatric section of a general hospital. Introduced during an epidemic of severe staphylococcal pneumonia and bronchiolitis in younger children, ALTAFUR was employed in treating a total of 59 infants or juvenile patients, most of whom had upper or lower respiratory tract involvement. Almost all had been given antibiotics without effect; 34 were judged severely or critically ill. Cures were obtained in 54 of these patients after a 3 to 10 day course of ALTAFUR. There was only one failure (results were inconclusive in the remaining four cases). Mixed infections with *Pneumococcus* or *Streptococcus* sp. also responded readily.

ALTAFUR was administered orally in varying dosage: the optimal dose is believed to be about 22 mg./Kg. daily.

Side effects were minimal in these patients, being limited to gastric intolerance in a few cases, usually controllable by giving the drug with or after meals. Laboratory studies performed before and after ALTAFUR treatment revealed no adverse influence on renal, hepatic or hematopoietic function, nor other signs of toxicity.

In vitro, staphylococci isolated in this series proved uniformly susceptible to ALTAFUR, whereas many strains were resistant to a variety of antibiotics. With ALTAFUR as with all nitrofurans, the lack of development of significant bacterial resistance is considered a major advantage over other antimicrobials.

Lysaught, J. N., and Cleaver, W.: Paper presented at the Symposium on Antibacterial Therapy, Michigan and Wayne County Academies of General Practice, Detroit, Sept. 12, 1959 (published Nov., 1959)



bright new star  
in the antibacterial firmament

# ALTAFUR<sup>T.M.</sup>

brand of furaltadone

the first nitrofurantoin effective orally  
in systemic bacterial infections

- Antimicrobial range encompasses the majority of common infections seen in everyday office practice and in the hospital
- Decisive bactericidal action against staphylococci, streptococci, pneumococci, coliforms
- Sensitivity of staphylococci in vitro (including antibiotic-resistant strains) has approached 100%
- Development of significant bacterial resistance has not been encountered
- Low order of side effects
- Does not destroy normal intestinal flora nor encourage monilial overgrowth (little or no fecal excretion)

Tablets of 50 mg. (pediatric) and 250 mg. (adult)

Average adult dose: 250 mg. four times a day, with food or milk

Pediatric dosage: 22-25 mg./Kg. (10-11.5 mg./lb. body weight daily in 4 divided doses)

CAUTION: The ingestion of alcohol in any form, medicinal or beverage, should be avoided during Altafur therapy.

NITROFURANS—a *unique* class of antimicrobials

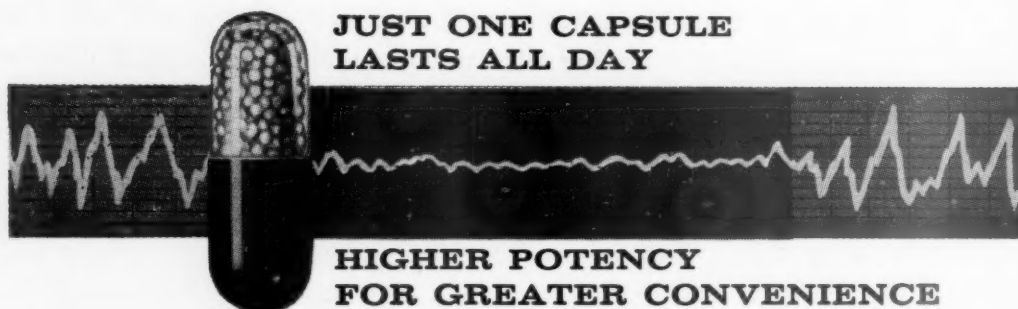
EATON LABORATORIES, NORWICH, NEW YORK

**NEW AND EXCLUSIVE**

**FOR SUSTAINED  
TRANQUILIZATION**

MILTOWN® (*meprobamate*) now available  
in 400 mg. continuous release capsules as

**Meprospan®-400**



- relieves *both* mental and muscular tension without causing depression
- does not impair mental efficiency, motor control, or normal behavior

**Usual dosage:** One capsule at breakfast,  
one capsule with evening meal

**Available:** *Meprospan-400*, each blue capsule contains  
400 mg. Miltown (*meprobamate*)  
*Meprospan-200*, each yellow capsule contains  
200 mg. Miltown (*meprobamate*)  
*Both potencies in bottles of 30.*

**W** WALLACE LABORATORIES, *New Brunswick, N. J.*

CME-8427

*the true specific  
for  
monilial vaginitis*

# GENTIA-JEL<sup>®</sup>

*CURES ARE QUICKER* Gentia-jel's unsurpassed monilia-killing power results in quicker cures and less recurrence. *IMMEDIATE RELIEF* This soothing jel provides fast, gratifying relief of vulvar itching and burning . . . destroys fungi and bacteria. *COMPLETE COVERAGE* Gentia-jel disperses completely over vaginal and cervical mucosa, penetrates into all folds and bathes the vulvar labia.



*start therapy  
with GENTIA-JEL  
. . . it works  
when others fail*

WESTWOOD PHARMACEUTICALS

Buffalo 13, New York



# GENTIA-JEL

*the true specific  
for monilial vaginitis*

Gentian violet is the most effective agent known for the destruction of *Monilia albicans*. Numerous nonstaining preparations have been used in treating vaginal moniliasis but have proven far less effective than gentian violet.

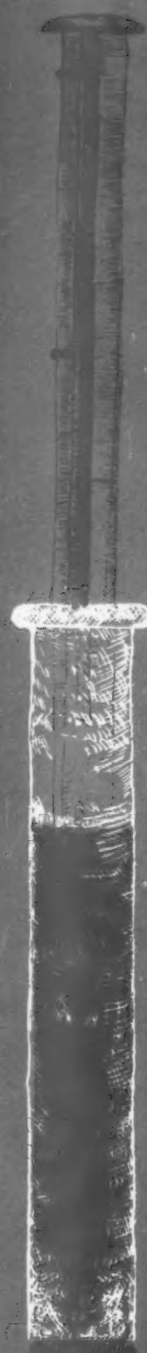
Gentia-jel's effectiveness is proved by its rate of cures during the last trimester of pregnancy, when mycotic infections are most difficult to cure. Gentia-jel is shown to be over 93% clinically effective, and has been used successfully in hundreds of cases refractory to other therapies.

Monillial reinfection is avoided with Gentia-jel by eliminating two major causes: (1) there is no manual introduction of tablets or suppositories into the vagina and (2) applicators are never re-used, but discarded.

And, Gentia-jel is easy for your patients to use. (1) Prior to retiring for the night, patients lie back with knees flexed, insert applicator and instill Gentia-jel. (2) Applicator is removed and discarded and a vaginal tampon or pledget of cotton is inserted in the introitus. A sanitary pad should be worn.

Treatment should be continued over 12 days to assure a negative smear.

Gentia-jel is supplied in packages of 12 single-dose disposable applicators.



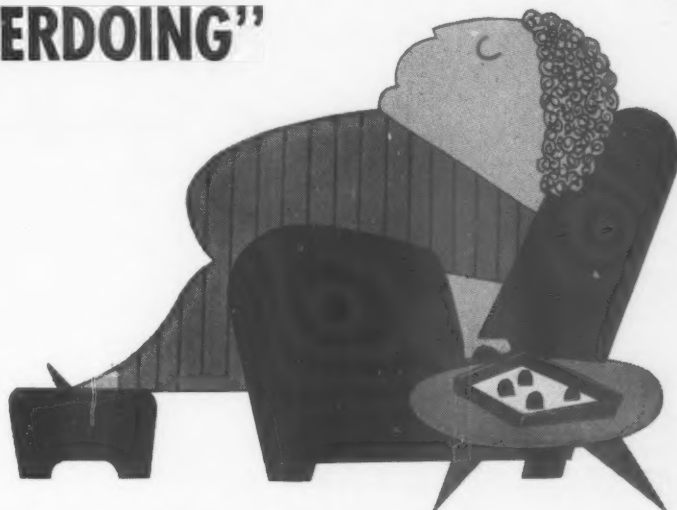
**WHY WAIT UNTIL OTHER THERAPIES FAIL...  
START YOUR PATIENTS WITH GENTIA-JEL**

WESTWOOD PHARMACEUTICALS

Buffalo 13, New York

predictable weight loss

FOR THE VICTIM OF  
OVEREATING AND  
"UNDERDOING"



Rx

# BIPHETAMINE®

A 'STRASIONIC' RELEASE ANORETIC

RESIN

Employing 'Strasionic' release, Biphetamine's appetite appeasing, mildly invigorating action is uniformly prolonged for 10 to 14 hours with a single capsule dose. Caloric intake is reduced, energy output is increased. Weight loss is predictable—a comfortable 1-3 lbs. a week in 9 out of 10 cases.

"STRASIONIC  
RELEASE"  
MAKES THE  
**BIG**  
DIFFERENCE

## BIPHETAMINE® '20' Resin

Each black capsule contains:  
d-amphetamine ..... 10 mg.  
dl-amphetamine ..... 10 mg.  
as resin complexes



## BIPHETAMINE® '12½' Resin

Each black and white capsule contains:  
d-amphetamine ..... 6.25 mg.  
dl-amphetamine ..... 6.25 mg.  
as resin complexes



## BIPHETAMINE® '7½' Resin

Each white capsule contains:  
d-amphetamine ..... 3.75 mg.  
dl-amphetamine ..... 3.75 mg.  
as resin complexes



Single Capsule Daily Dose 10 to 14 hours before retiring

Rx Only. Caution: Federal law prohibits dispensing without prescription.

Biphetamine—made and marketed ONLY by **STRASENBURGH & LABORATORIES**  
ROCHESTER, N. Y., U. S. A.

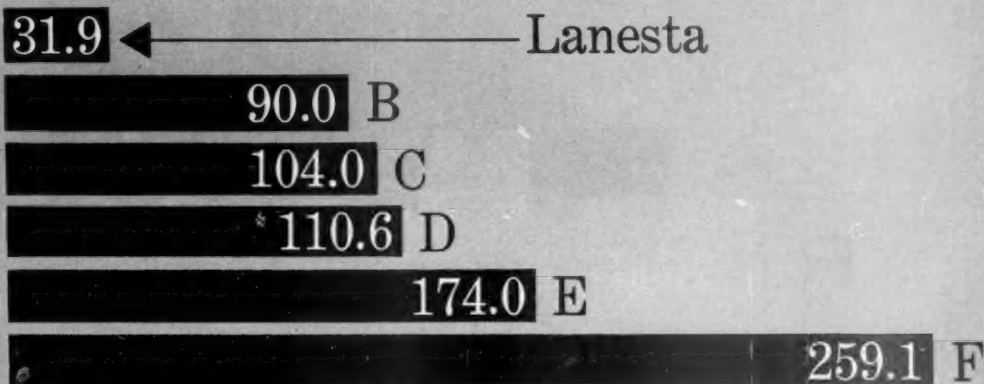
Originators of 'Strasionic' (sustained ionic) Release

# new Lanesta Gel

speedier spermicidal action

Spermicidal Time of Six Leading Contraceptive  
Jellies in Minutes<sup>1</sup>

Cytometer Chamber Spermatocidal Test



Mean Spermatocidal Time  $\pm$  S. E., Min.

Berberian, D. A., and Slichter, R. G.: J.A.M.A. 168:2257 (Dec. 27) 1958.

*4 active agents provide speed and efficacy...*

- 7-chloro-4-indanol, the new spermicide, rapidly and completely immobilizes sperm in concentrations as low as 1:4,000—yet is so mild that it may be used even in the presence of vaginal infection.
- 10% NaCl in ionic strength greatly accelerates spermicidal action.
- sodium lauryl sulfate acts as a dispersing agent and spermicidal detergent.
- ricinoleic acid acts as a sperm inactivator and immobilizer.

Lanesta Gel® with diaphragm provides the most effective means of conception control. However, if a patient is unwilling or unable to use a diaphragm, Lanesta Gel provides faster spermicidal action—plus desirable occlusion at the cervical os when used alone.

Supplied: Lanesta Exquiset (Physician's Prescription Package), 3 oz. tubes with applicator; 3 oz. refills. Available at all pharmacies.

References: 1. Berberian, D. A., and Slichter, R. G.: J.A.M.A. 168:2257 (Dec. 27) 1958. 2. Bailey, J. H.; Coulston, F., and Berberian, D. A.: J. Am. Pharm. A. (Sc. Ed.) 48:212 (April) 1959. 3. Gamble, C. J.: Am. Pract. & Digest Treat. 9:1818 (Nov.) 1958. 4. Berberian, D. A.; Coulston, F., and Slichter, R. G.: Toxicol. & Appl. Pharmacol. 1:366 (July) 1959. 5. Warner, M. P.: J. Am. M. Women's A. 14:412 (May) 1959.

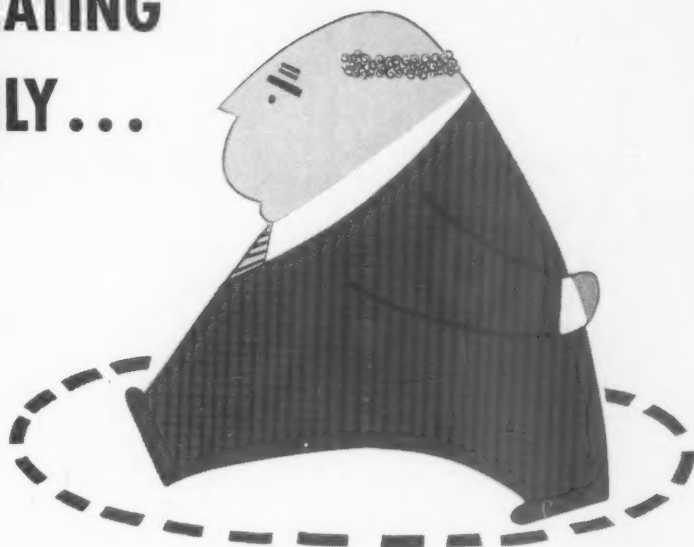
Distributed by GEORGE A. BREON & CO., New York 18, N. Y.  
Manufactured by Esta Medical Laboratories, Inc., Alliance, Ohio

P.S. *Lanestein® is also available.*



**predictable weight loss**

**FOR THE VICTIM OF  
OVEREATING  
ONLY...**



**Rx**

**NEW**

# IONAMIN<sup>TM</sup>

A 'STRASIONIC' ANORETIC

PHENYL-TERT.-BUTYLAMINE RESIN

Employing 'Strasionic' release, Ionamin's appetite appeasing action is uniformly prolonged for 10 to 14 hours with a single capsule dose. Caloric intake is reduced to a level consistent with the energy output of an "active" overeater. Weight loss is predictable—a comfortable .221 pounds per day in average cases.

**"STRASIONIC  
RELEASE"  
MAKES THE  
BIG  
DIFFERENCE**

Rx Only.

Caution: Federal law prohibits dispensing without prescription.

**IONAMIN<sup>TM</sup>  
'30'**

Each yellow capsule contains:  
phenyl-tert.-butylamine . . 30 mg.  
as a resin complex



**IONAMIN<sup>TM</sup>  
'15'**

Each grey and yellow capsule contains:  
phenyl-tert.-butylamine . . 15 mg.  
as a resin complex



**Single Capsule Daily Dose 10 to 14 hours before retiring**

**Ionamin—made and marketed ONLY by**

**STRASBURGH LABORATORIES**  
ROCHESTER, N. Y., U. S. A.

Originators of 'Strasionic' (sustained ionic) Release



# FOR EASIER ELIMINATION IN OBSTETRICS OR SURGERY



## TARGET ACTION

*specifically on the large bowel*

### **DORBANE®**

(1, 8-dihydroxyanthraquinone)

selective peristaltic stimulant • smooth, overnight action  
• no griping • well tolerated • non-habituating

Available in 75 mg. scored tablets and suspension.

WHERE STOOL SOFTENING IS ALSO INDICATED

### **DORBANTYL® FORTE**

(Dorbane, 50 mg. + dioctyl sodium sulfosuccinate, 100 mg.)\*

Double-strength capsules for maximum economy and convenience.

### **DORBANTYL®**

For lower dosage and in children.  
Available in capsules and suspension.

(Dorbane, 25 mg. + dioctyl sodium sulfosuccinate, 50 mg.)\*

\*In proportions proved optimal by clinical trial in over 540 cases.  
(Marks, M. M.: Clin. Med. 4:151, 1957.)

*SchenLabs*

SCHENLABS PHARMACEUTICALS, INC. • NEW YORK 1, N. Y. Manufacturers of NEUTRAPEN® for penicillin reactions.



**Check cough 8-12 hours**



**with a single dose**

# Rx TUSSIONEX®

A 'Strasionic' Antitussive • Dihydrocodeinone Resin—Phenyltoloxamine Resin

"STRASIONIC  
RELEASE"  
MAKES THE  
**BIG**  
DIFFERENCE

- Permits Natural Discharge of Mucus
- Predictable Antitussive Action
- Minimum Amount of Narcotic

**TWO FORMS:** Tussionex Thixaire™ Suspension • Tussionex Tablets

Each teaspoonful (5c.c.) or tablet provides 5 mg. dihydrocodeinone and 10 mg. phenyltoloxamine as resin complexes.

Dose: 1 teaspoonful or tablet q 12 h. Children under 1 year, ¼ teaspoonful q 12 h; 1-5 years, ½ teaspoonful q 12 h.

Rx only. Class B taxable narcotic.

Tussionex—made and marketed only by

**STRASBURGH LABORATORIES**  
ROCHESTER, N. Y., U. S. A.

Originators of 'Strasionic' (sustained ionic) Release



NEW

ESKATROL\*

brand of dextro amphetamine and prochlorperazine

SPANSULE®

brand of sustained release capsules

to help your overweight "problem" patients stay on the

'Eskatrol' *Spansule* capsules combine:

- |   |   |
|---|---|
| • Dexedrine® 15 mg.<br>brand of dextro amphetamine<br>sulfate | the time-tested agent for the<br>control of appetite in weight<br>reduction                                 |
| • Compazine® 7.5 mg.<br>brand of prochlorperazine             | to counteract the emotional<br>stress which is frequently<br>associated with overeating<br>and with dieting |

A single 'Eskatrol' *Spansule* capsule taken in the morning:

1. curbs the appetite
2. relieves the basic emotional stress
3. imparts a sense of well-being

throughout the day—with a negligible incidence  
of restlessness and insomnia.

\*Trademark



stay on their diets, even for prolonged periods of time

### Clinical Experience with 'Eskatrol' *Spansule* capsules

During more than a year's clinical trials 'Eskatrol' was evaluated in more than 3000 patients. Side effects were mild and transitory.

In one controlled series of more than 200 patients, for example, nervousness—the most frequent complaint with other anti-appetite preparations—troubled only 5% of patients. Only 4.6% experienced insomnia—an incidence very close to placebo level. Eighty-two per cent experienced weight loss, which averaged 1.5 pounds per week. Seventy-two per cent were emotionally improved.

#### One particularly outstanding finding dominated the reports of these trials:

The patients who benefited particularly from 'Eskatrol' were those who depended on food for psychologic release. 'Eskatrol' relieved the emotional stress which had forced these patients to abandon earlier reducing measures, and enabled them to live with their diets—even for prolonged periods (often, for longer than six months).

*Prescription Size: Bottles of 30 capsules.*

*Smith Kline & French Laboratories, Philadelphia*



**reduce the risk  
of neonatal hemorrhage**

# Mephyton<sup>®</sup>

vitamin K<sub>1</sub>

**"has a more prompt, more potent and more prolonged effect than the vitamin K analogues"\***

- helps prevent hypoprothrombinemia, the most common cause of neonatal hemorrhage
- helps reduce incidence of intracranial hemorrhage due to hypoprothrombinemia

*Supply:* Tablets 5 mg.; bottles of 100. Emulsion, 1-cc. ampuls containing 10 mg. and 50 mg. per cc.; boxes of 6 ampuls.

*For additional information, write Professional Services, Merck Sharp & Dohme, West Point, Pa.*

\*Council on Drugs: New and Nonofficial Drugs, Philadelphia, J. B. Lippincott Co., 1969, p. 661.



**MERCK SHARP & DOHME, DIVISION OF MERCK & CO., INC., PHILADELPHIA 1, PA.**

MEPHYTON IS A TRADEMARK OF MERCK & CO., INC.



advancing with surgery

ETHICON®






reverse cutting

ATRALOC NEEDLES

20% more strength

ETHICON®



even in  
the first  
trimester

Even in the first few months of pregnancy, when nausea and vomiting is such a problem, 'Feosol' *Spansule* capsules provide strikingly effective and convenient iron therapy . . . with virtually none of iron's side effects.

In a representative series of pregnant patients, 83% had good to excellent hematinic response. G.I. distress was negligible. Patient acceptance was extraordinarily high.



only 1  
capsule  
q12h

FEOSOL<sup>®</sup>

brand of ferrous sulfate

SPANSULE<sup>®</sup>

brand of sustained release capsules

# GREATER PATIENT COMFORT and safety with **DYCLONE**<sup>TM</sup> dyclonine hydrochloride

the unsurpassed topical anesthetic

for  
instrumentations  
examinations  
pain  
pruritus

DYCLONE does more...safely...than any  
other topical anesthetic because it is

fast-acting  
long-acting  
antibacterial  
antifungal  
nonsensitizing

supply...Dyclone Creme, tubes of 1 oz. with  
rectal applicator. Dyclone Solution, bottles  
of 1 and 8 oz.



**PITMAN-MOORE COMPANY**  
DIVISION OF ALLIED LABORATORIES, INC.  
INDIANAPOLIS 6, INDIANA



they can plan their own home...

but they need your help in planning their family

**Delfen<sup>®</sup>**  
VAGINAL CREAM

THE MODERN CHEMICAL SPERMICIDE

**Preceptin<sup>®</sup>**  
VAGINAL GEL

THE SPERMICIDAL GEL WITH BUILT-IN BARRIER

**PRESCRIBED WITH CONFIDENCE FOR SIMPLE, EFFECTIVE CONTRACEPTION**

87859



Does more than curb appetite...  
also relieves the tensions of dieting



# new! Appetrol®

DEXTRO-AMPHETAMINE + MILTOWN®

## Helps you keep your patient on your diet

AN EXTENSIVE SURVEY shows that in 68% of overweight persons there is an emotional basis for failure to limit food intake.<sup>1</sup> Appetrol has been formulated to help you overcome this problem and to keep your overweight patient on your diet.

THIS NEW ANORECTIC does more than give you dextro-amphetamine to curb your patient's appetite. It also gives you Miltown to relieve the tensions of dieting which undermine her will power.

IN PRESCRIBING APPETROL, you will find that your patient is relaxed and more easily managed so that she will stay on the diet you prescribe.

**Usual dosage:** 1 or 2 tablets one-half to 1 hour before meals.

**Each tablet contains:** 5 mg. dextro-amphetamine sulfate and 400 mg. Miltown (meprobamate, Wallace).

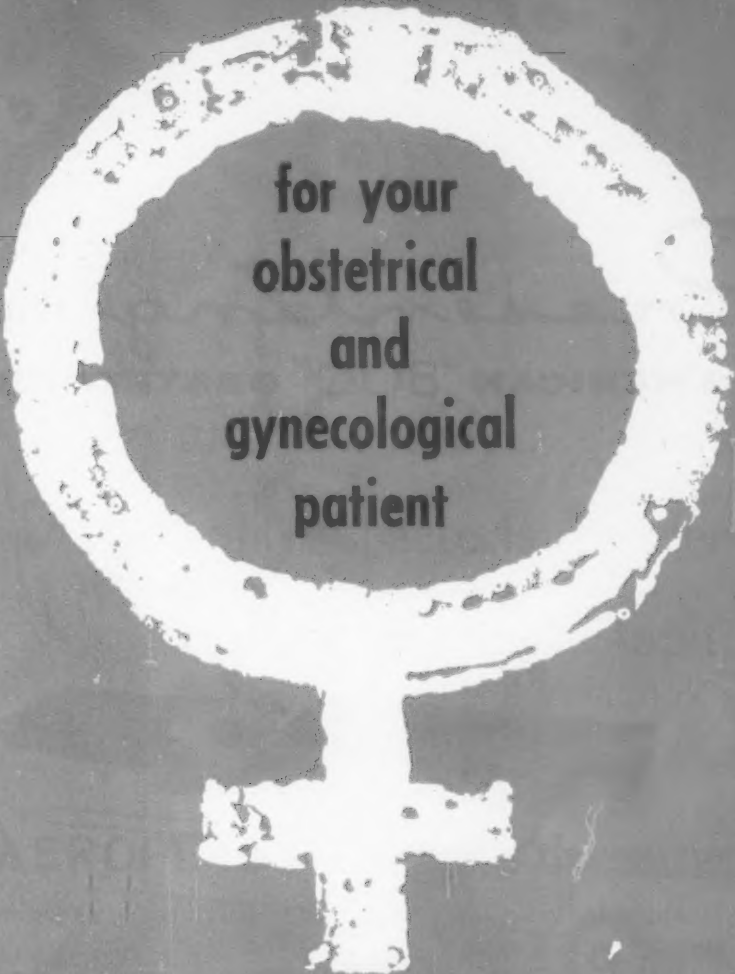
**Available:** Bottles of 50 pink, uncoated tablets.

1. Kotkov, B., Group psychotherapy with the obese. Paper read before The Academy of Psychosomatic Medicine, October 1958.



WALLACE LABORATORIES, New Brunswick, N. J.

CPL-318



for your  
obstetrical  
and  
gynecological  
patient

## BACULIN

VAGINAL TABLETS

FUNGICIDAL . . . BACTERICIDAL . . . PROTOZOICIDAL COMPREHENSIVE  
TREATMENT OF VAGINAL INFESTATION.

*A single BACULIN vaginal tablet generally destroys the causes of vaginitis, namely Trichomonas Vaginalis, Candida Albicans, and non-specific organisms. Prescribe BACULIN vaginal tablets in your next case of non-venereal vaginitis.*

## desplex

ANTIABORTIVE

ACCIDENTS OF PREGNANCY CAN NOT BE CURED. THEY MUST BE PREVENTED.  
desplex IS A CLINICALLY PROVED ANTIABORTIVE.

desplex, a unique combination of ultramicronized diethylstilbestrol and vitamins C, and B complex, was shown 96% effective in carrying 1200 difficult pregnancies to term.<sup>1</sup> For assurance of a successful pregnancy, prescribe desplex tablets.  
Now contains hesperidin complex.

## BANAUSEA

TABLETS

ANTINAUSEANT, ANTIEMETIC — BAN NAUSEA AND VOMITING OF PREGNANCY  
. . . SAFELY . . . EFFECTIVELY . . . ECONOMICALLY.

*Just prescribe BANAUSEA tablets, one upon arising and one at bedtime. Turn your patients' blue mornings pink with BANAUSEA tablets.*

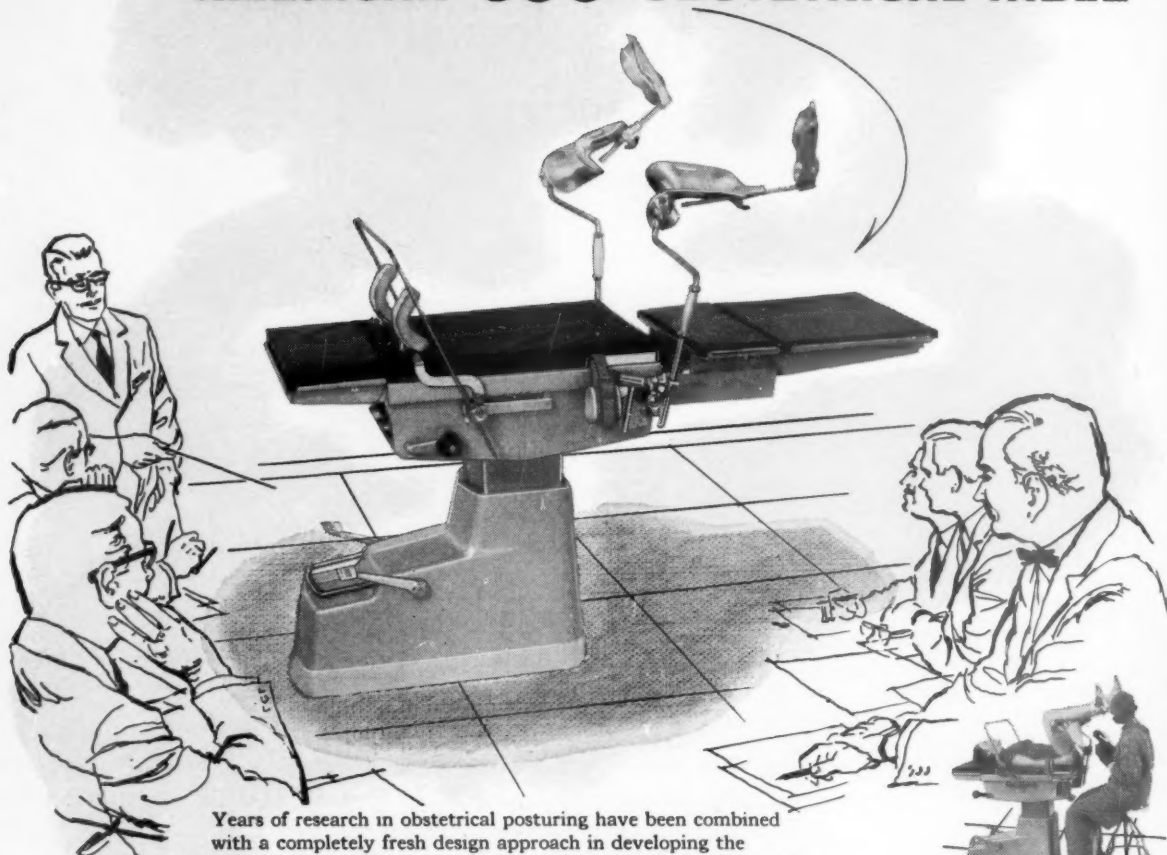
*Samples upon request.*

*Reference: I. Peña, E. F., Med. Times, 82-921, 1954.*



Amfre-Grant, Inc., Brooklyn 26, N. Y.

# Presenting THE ALL NEW AMERICAN "800" OBSTETRICAL TABLE



Years of research in obstetrical posturing have been combined with a completely fresh design approach in developing the Amsco "800" table. The result is an obstetrical table so compact, so maneuverable and so efficient as to be truly revolutionary in its advantages for operative as well as perineal route delivery.

From the narrow, flowing lines of the flexible top to the permanent or portable power base . . . the "800" is new.

## Every Feature ~

- finger-tip controls
- retractable foot section
- retractable 12" delivery shelf
- ratchet type legholder sockets
- flexible head and foot sections
- wide perineal opening for postpartum drainage

. . . each is new, exclusive and vital to the convenience of the obstetrician and the welfare of the patient.

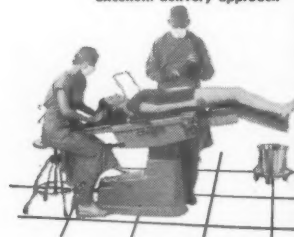
Every hospital and every obstetrician will have a direct interest in this dramatically better table. Fully illustrated brochure TC-224-R is available without obligation.



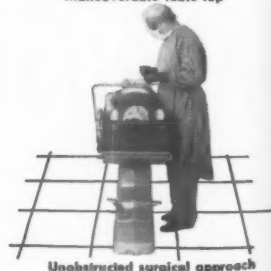
**AMERICAN  
STERILIZER**  
ERIE • PENNSYLVANIA

World's largest designer and manufacturer of Sterilizers, Operating Tables, Lights and related hospital equipment

Excellent delivery approach



Maneuverable table top



Unobstructed surgical approach





*after surgery...*

apply a bacterial barrier  
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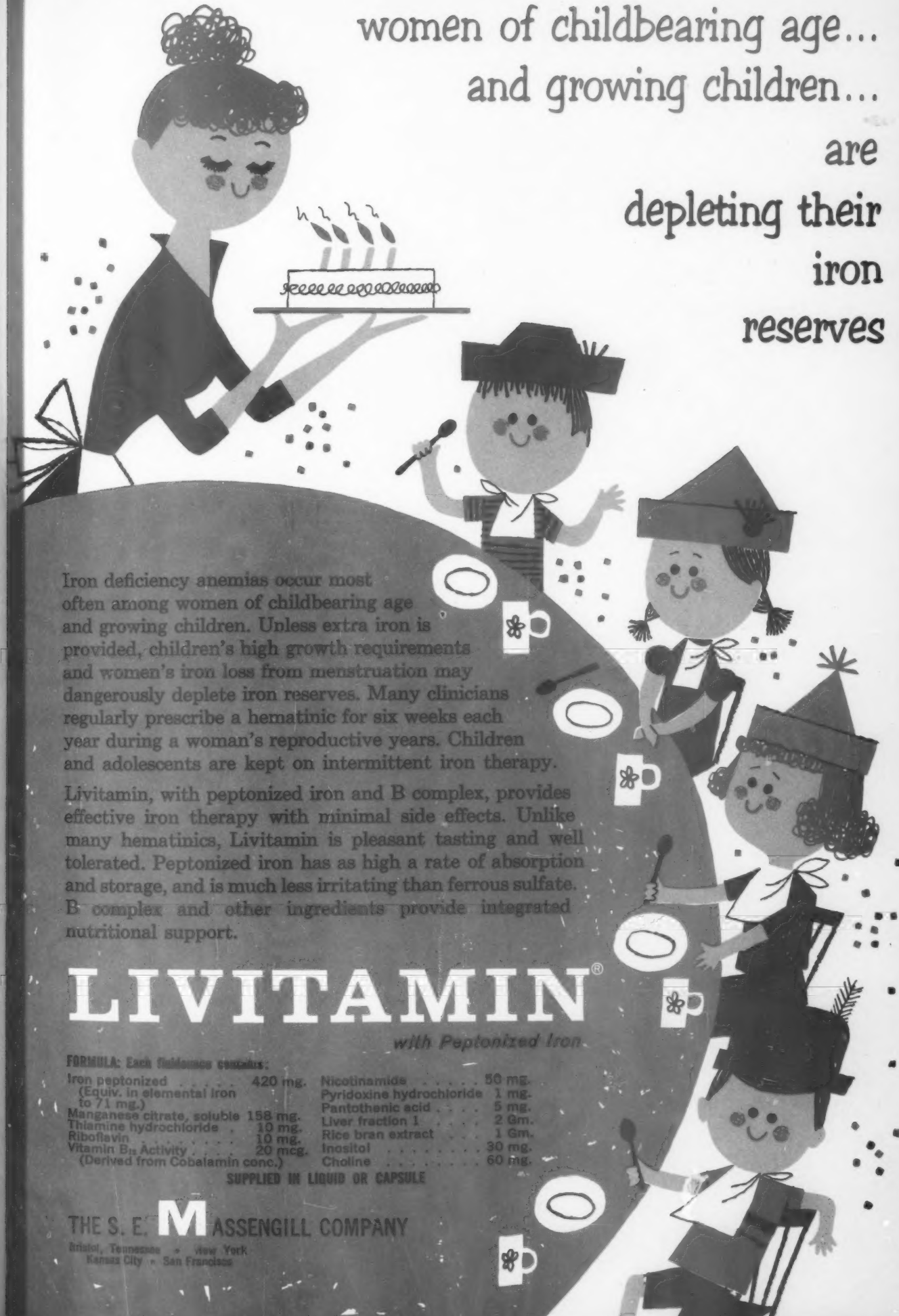
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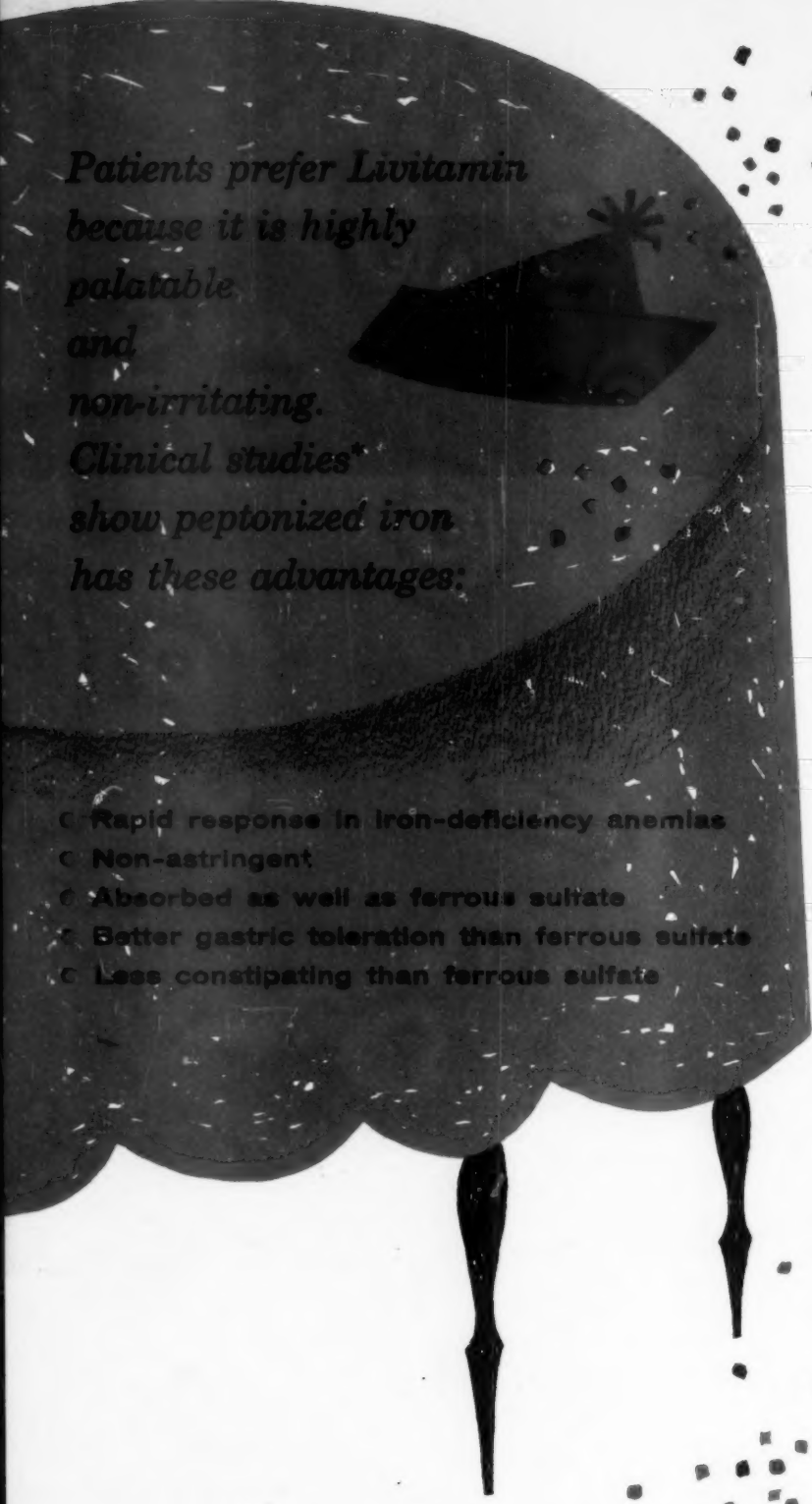
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## American Journal of Obstetrics and Gynecology

### GYNECOLOGY

#### Blood dyscrasia as a causative factor in abnormal uterine bleeding

H. MELVIN RADMAN, M.D.

*Baltimore, Maryland*

THE variety of causes behind abnormal uterine bleeding has perplexed gynecologists for a long time. Since primitive times psychic shock or emotional upsets have been known to produce irregular or profuse uterine bleeding.<sup>13</sup> In addition to the psychogenic factors, the possibilities of organic lesions such as carcinoma, fibromyoma, endocrine dysfunction, and bleeding associated with intra- or extrauterine pregnancy must always be considered. It has become increasingly apparent that abnormalities in the blood-clotting mechanism or deviation from the normal hemopoietic phenomenon has been a causative factor. Menometrorrhagia is often considered to be a symptom of pelvic pathology. The fact that it may re-

sult from a constitutional blood disorder is either overlooked or forgotten.<sup>2</sup>

Many investigators believe that the onset of irregular or profuse bleeding may be the first manifestation of a blood dyscrasia.<sup>7</sup> The occurrence of an antihemophilic globulin defect associated with prolonged uterine bleeding was first recognized by Alexander and Goldstein.<sup>3</sup> Singer and Ramot<sup>20</sup> were able to find 14 such instances. Thomas, Black, and Perry<sup>23</sup> reported the case of a woman, aged 24, with severe menorrhagia due to hemophilia, who required twelve transfusions. She bled in her antepartum period, and after delivery she had a severe postpartum hemorrhage. In 1951 Merskey<sup>15</sup> as well as Israels<sup>11</sup> reported authenticated cases of hemophilia in a woman. Taylor and Biggs<sup>22</sup> have found that occasionally the female carriers of hemophilia have an unusual tendency to bleed, themselves.

*From the Department of Gynecology  
Sinai Hospital of Baltimore.*

Hematological abnormality is known to occur in women much more frequently than in men, in a proportion of three to one. Pohle<sup>16</sup> and Dameshek and Rheingold<sup>7</sup> accounted for this by finding a decrease in platelet formation in women, beginning 14 days prior to the onset of the menses.

In contrast to most observers, Barnes<sup>4</sup> felt that constitutional hemorrhagic tendencies were not a factor in patients suffering from hypermenorrhea. Following a thorough 3 year study of these patients, he concluded that women with blood dyscrasia will not acquire excessive vaginal bleeding without the intermediary of a local pelvic condition. The latter usually would have been sufficient to explain the bleeding on an organic basis.

It has been axiomatic that menstrual blood under normal circumstances has little or no clotting mechanism. It is understandable, however, that this physiological condition could be altered by changes in the circulating blood coagulability.

Buxton demonstrated that at least 11 per cent<sup>6</sup> of female patients suffering from a blood dyscrasia had some deviation of the menstrual function. Israel and Mendell,<sup>10</sup> Kahn,<sup>12</sup> Reich, Nechtow, Kurzon, and Mercer,<sup>19</sup> and Hegedus and Anderson<sup>9</sup> found that excessive and irregular bleeding were prominent symptoms in patients with purpura hemorrhagica, leukemia, aplastic anemia, and splenic anemia. Haden and Singleton<sup>8</sup> revealed that even with simple achlorhydric anemia, 11 of 29 patients had disturbances of the menses.

It is the purpose of this report to accentuate and stress the fact that general hemorrhagic tendencies may produce menstrual aberrations. Although the relative frequency is not great, it is illogical to pursue the study of a patient with menstrual irregularities without a complete knowledge of the blood picture.

Heretofore most of the studies concerning menometrorrhagia resulting from blood dyscrasias have involved patients with thrombocytopenic purpura. Other types of abnormalities in the blood-clotting mechanism have been known to produce the same

effects. One of the more unusual types of hemorrhagic tendencies may be found in those patients suffering from Christmas disease. Biggs and Macfarlane<sup>5</sup> demonstrated a hemophiliac-like disease whose chief distinguishing characteristic was the inability of the blood to clot. While this disease is clinically undistinguishable from hemophilia, it is due to a deficiency of a clotting factor that is different from antihemoglobulin. The hereditary factor of Christmas disease is identical with hemophilia and, as in this entity, it may arise spontaneously. It is of the utmost importance that Christmas disease be differentiated from true hemophilia. This may be accomplished by the thromboplastic component. Since the recognition of this disease, many cases have been discovered and recorded in the literature.<sup>14</sup> Ratnoff<sup>18</sup> has reported the changes in Christmas factor associated with pregnancy, and Aball<sup>1</sup> has studied its course in the neonatal period. The following is a report of Christmas disease in a patient who came to our attention because of excessive bleeding after a simple gynecological procedure.

Mrs. J. B., aged 35, was first seen by Dr. Milton Sachs because of excessive bleeding following electrocauterization for a simple erosion of the cervix. She also had profuse bleeding from the gums after root canal dentistry. The past history revealed that she had had 3 normal pregnancies, labors, and deliveries. At no time in her menstrual life had she experienced any abnormalities of the periods. The family history gave no additional pertinent information. Five months after her last delivery, electrocauterization was done because of a simple erosion of the cervix. Within a week of this procedure there was prolonged profuse bleeding from the cervix that could be controlled only by repeated vaginal packing. However, she recovered without event except for severe secondary anemia. Shortly after this she had some root canal work done. This, in turn, was followed by profuse bleeding from the gums. In view of the history of bleeding, she was admitted to the hospital. A hematological investigation including a thromboplastic generation test revealed plasma thromboplastic deficiency compatible with the diagnosis of Christmas disease.

A blood transfusion resulted in the alleviation of the hemorrhagic tendencies.

Gaucher's disease is another type of blood dyscrasia which may be accompanied by abnormal uterine bleeding.<sup>17</sup> The following is an illustrative report.

Mrs. M. B., aged 26, was seen in July, 1956, when she was in the first trimester of her first pregnancy. The past history revealed that she was known to have had Gaucher's disease since the age of 11. Her sister (a resident of New York City) also had this disease although neither the parents nor grandparents had been so afflicted. Upon physical examination, the pertinent finding was an enlarged spleen extending 17 cm. below the costal margin. The pelvic examination confirmed the presence of an early intrauterine pregnancy. There was x-ray evidence of Gaucher's disease in the long bones of the extremities; sternal puncture showed the presence of Gaucher's cells. The pregnancy progressed to term despite the enormous enlargement of the spleen. She was delivered of a normal, well-developed male child by low forceps, without incident. To this date the child has failed to show any evidence of Gaucher's disease. On the patient's third postpartum day there was an episode of profuse vaginal bleeding. This was readily controlled by 500 c.c. of citrated blood. Her subsequent course has been uneventful; her menses have returned to normal limits.

#### Comment

As a whole, the problem of abnormal uterine bleeding is a complicated one inasmuch as it is often difficult to determine an exact causative factor. Stress must be placed on the fact that this bleeding should not be considered an entity in itself but rather a symptom complex.<sup>21</sup> Many authorities consider the onset of irregular or profuse vaginal bleeding to be the first manifestation of some type of blood dyscrasia. We are in accord with this opinion. In pursuing the study of these patients it is well to remember that excessive menstrual bleeding may be associated with severe nose bleeds, and bleeding from the gums and other mucous membrane surfaces. In some cases, however, menorrhagia is the sole manifesta-

tion and may be so outstanding that attention is focused on the possibility of a local lesion. Recent investigations have proved that women also may have hemophilia or hemophiliac-like diseases. With this in mind, it becomes increasingly important to complete our study of these patients with a thorough knowledge of the blood picture. It is unfortunate that, at times, patients with abnormal bleeding have been treated without prior investigation into the possibilities of hemorrhagic diseases. Such a procedure has been followed by unnecessary or even harmful operations that apparently could have been avoided. Dameshek and Rheingold<sup>7</sup> have emphasized this point and have advanced a few diagnostic tests which they feel may help to establish the proper diagnosis. These are the tests as outlined:

#### 1. Examination of a stained blood smear.

It is felt that examination of the smear is of even better diagnostic value than a platelet count. Normally, platelets are present both in clumps and singly in every oil immersion field. With moderate reduction, clumps are rarely seen, and only 3 to 6 single platelets are found. With marked reduction, platelets are rarely seen. In addition to data on the platelets, the blood smear may also reveal abnormalities in the leukocytes and the red blood cells.

#### 2. Determination of the bleeding time.

Bleeding times in excess of 5 minutes are considered abnormal.

**3. The tourniquet test.** The blood pressure cuff is applied and kept inflated for 15 minutes. The number of petechiae present in a circle 2.5 cm. in diameter and 4 cm. below the elbow are counted.

**4. The clot retraction determination.** This is studied by observation of 1 c.c. of blood at intervals of 30 minutes, one hour, and 24 hours. Normally, retraction begins in 30 minutes and is complete in 3 to 24 hours.

While it is not within the province of the gynecologist to be expert in the determination of blood dyscrasias, it is important that he be acquainted with the fundamentals of their detection. If the diagnostic procedures prove to be conclusive or not,



further investigation can always be pursued. As has been pointed out,<sup>2</sup> even the finding of a pelvic lesion which would seem to "explain" the menstrual bleeding does not necessarily eliminate the need for hematologic study. When patients with known blood dyscrasias become pregnant or have gynecological operative procedures, one must constantly be alert to the potentiality of abnormal bleeding from the reproductive tract and consequently be prepared to handle such emergencies.

### Summary and conclusions

1. In considering abnormal uterine bleeding one must be aware that abnormalities

in the blood-clotting mechanism or deviations from the normal hemopoietic phenomenon may be causative factors.

2. In addition to the common blood dyscrasias, the possibility of hemophilia or hemophilic-like diseases as causative factors in producing menstrual aberration must also be considered.

3. Case reports of patients suffering from Christmas disease and Gaucher's disease having abnormal bleeding have been presented. In both instances there was no evidence of a lesion in the uterus, tubes, or ovaries.

4. A thorough investigation of the blood picture is of prime importance in studying patients with abnormal uterine bleeding.

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# Coagulation studies of patients with abnormal uterine bleeding

ARTHUR J. SEAMAN, M.D.

RALPH C. BENSON, M.D.

Portland, Oregon

THERE are three questions each gynecologist must ask himself before performing a laparotomy or dilatation and curettage because of abnormal uterine bleeding: (1) Is there an underlying hemorrhagic diathesis? (2) Will surgical procedures result in further hemorrhage and hazard to life? (3) Will one harm this patient by trying to offer operative help?

This paper reports our evaluation of a panel of screening tests designed to identify individuals with an abnormal bleeding tendency when localized bleeding itself seems the impelling indication for operation.

## Patients and methods

Forty-three women were studied. These included most of the patients with abnormal uterine bleeding seen during the past year who had no apparent gynecological lesions or evidence of constitutional disease.

Screening tests used routinely included the following:

1. *Bleeding time* (modified Duke method<sup>1</sup>). After the skin was cleansed with alcohol, the lateral aspect of the left fourth finger was pierced by the measured 3 mm. tip of a No. 11 Bard Parker knife protruding through a cork. The drops of blood (but not the skin) were touched at 30 second

intervals with a filter paper until no red staining occurred. The first failure to imprint was considered the end point.

2. *Thromboplastin time* (the "prothrombin time" of Quick<sup>2</sup>) modified by the employment of saline extract human brain thromboplastin.<sup>3</sup>

3. *P and P test* (the prothrombin and proconvertin combined activity) as described by Owren and Aas<sup>4</sup> with the exception that barium sulfate adsorbed bovine plasma was used as the substrate.

4. *Partial thromboplastin time* (P.T.T.)<sup>5</sup> with an homogenized suspension of Asolectin as the partial thromboplastin.

5. *Clot retraction*. Observed at 1, 2, and 24 hours, 3 ml. of blood was incubated in a conical glass tube. A wire hook was suspended from the cork into the blood prior to coagulation.<sup>6</sup>

Specialized test methods for the further clarification of defects of patients with abnormal screening test results included:

1. *Thromboplastin generation test* of Biggs and Douglas<sup>7</sup> modified by the use of an Asolectin suspension in place of a platelet suspension.

2. *Russell viper venom-cephalin method* of Hjort and associates<sup>8</sup> for the combined prothrombin and Stuart factor activity.

3. *Proconvertin assay method* of Owren<sup>9</sup> and Aas.<sup>10</sup>

4. *Proaccelerin assay* as previously described.<sup>11</sup>

5. *Antithrombin titer estimation* as described by Innerfield, Shub, and Boyd.<sup>12</sup>

*From the Departments of Medicine and Obstetrics and Gynecology, University of Oregon Medical School.*

*Presented before a meeting of the Western Society for Clinical Research, Carmel, California, Jan. 31, 1959.*

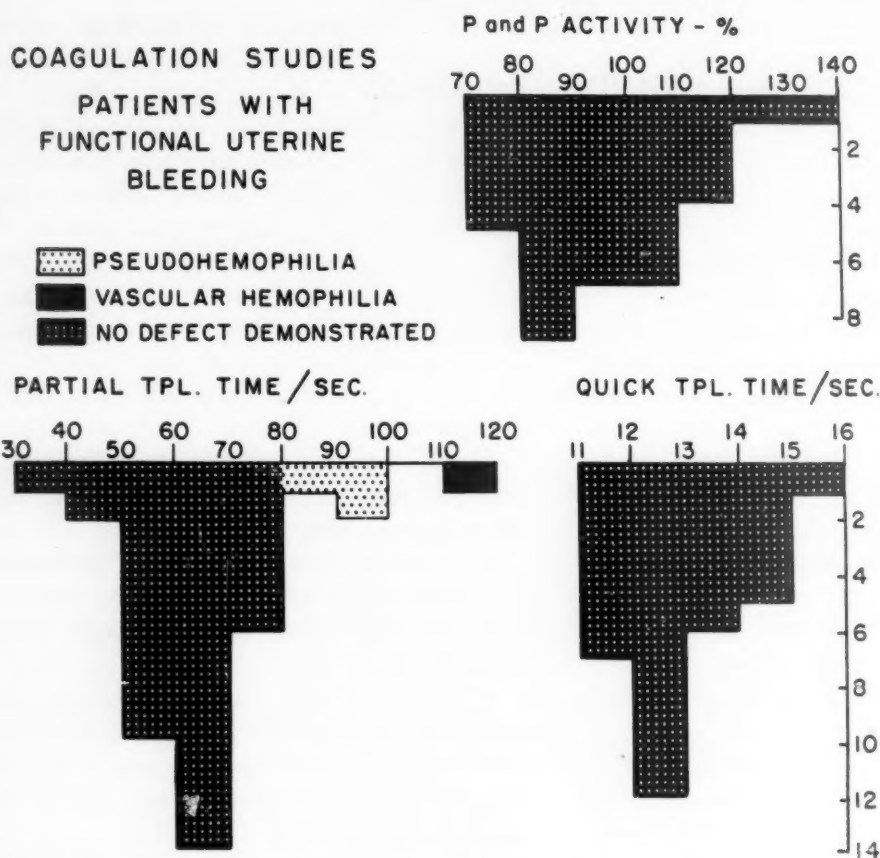


Fig. 1. Screening test results of plasma coagulation activities.

6. *Fibrinogen determination.* Citrated plasma, 0.5 ml., was diluted in saline to a total of 10 ml.; 1 ml. of bovine thrombin (200 units per milliliter) was added; 20 minutes later the clot was wound onto a glass rod. It was then transferred to a tube of physiological saline, then to water, next to acetone, and finally to ether. It was then dried in an oven and weighed directly as fibrin on a Mettler electronic scale. A value was then calculated for the milligrams of fibrinogen per 100 ml.<sup>13</sup>

7. *Euglobulin lysis time of Von Kualla and Schultz.*<sup>14</sup>

### Results

**Screening tests.** An abnormally prolonged bleeding time was demonstrated in 6 of 43 patients with abnormal uterine bleeding. Partial thromboplastin times were prolonged in 4 of these 6 patients (Fig. 1).

No abnormalities were detected by the thromboplastin time (Quick), by the P and P test, or by clot retraction study in this group of patients with uterine bleeding.

**Additional studies.** Three of the 4 patients with abnormal partial thromboplastin times had abnormal thromboplastin generation test results. Patient 1 had a plasma factor defect and her plasma was unable to correct the abnormal thromboplastin generation of an individual with known antihemophilic globulin deficiency. Patients 2 and 3 had abnormal serum thromboplastin generation defects that were incapable of mutual correction. However, both these sera corrected the defects of PTC deficient sera. The plasma of both these patients had normal Russell viper venom-cephalin times which mitigated against Stuart factor deficiency. Both of these patients additionally exhibited fibrinogenopenia. Two members

of the family of Patient 3 demonstrated partial expressions of the same defect. The mother had a borderline prolongation of bleeding time on one of two examinations and an abnormal serum thromboplastin generation defect. The maternal serum was unable to correct the serum thromboplastin generation defect of Patient 2. The brother of Patient 3 had an abnormally prolonged partial thromboplastin time and fibrinogenopenia although both his bleeding time and serum thromboplastin generation test results were normal (Table I).

Table I. Laboratory data summary

Patient	Screening tests		Other studies	
	Bleeding time	Partial thromboplastin time	Fibrinogen	Thromboplastin generation test defect
1	P	P	----	Plasma
2	P	P	Low	Serum
3	P	P	Low	Serum
4	P	P	Normal	None
5	P	N	----	None
6	P	N	----	None

#### Comments

Six of the 43 patients studied had prolonged bleeding times (Fig. 2). Because of a certain amount of skepticism expressed in the literature concerning the reliability of bleeding times, we compiled these values for all patients with suspected bleeding tendencies, other than uterine bleeding, examined during the same period. These are shown in Fig. 3. Prolonged bleeding times were encountered only in patients with just cause. The number of patients with pseudohemophilia in this second series was swelled by the examination of relatives of a patient with pseudohemophilia admitted for study because of repeated bouts of bleeding.

To test the constancy of the bleeding time determination, all 6 of the patients described in this report were examined on many occasions (from 4 to 48 times). The prolonged bleeding time was demonstrated

repeatedly in all. The bleeding times of the most frequently examined patient (Patient 1) are shown in Fig. 4. In the many determinations performed between July 29, 1957, and Jan. 12, 1959, only one bleeding time of this patient fell within normal limits. It was this patient who commented after our first performance of her bleeding time determination, "No wonder you got it longer than they always did before. You didn't put cotton on to stop it at three minutes."

As a further test of the pertinency of the prolonged bleeding time, questioning of the patients revealed that 5 of the 6 gave either a history of other family members' exhibiting abnormal bleeding or stated that they themselves had required transfusions for the treatment of postoperative hemorrhage (Table II). Only one of these patients (Patient 4) had had an uneventful operation (appendectomy, oophorectomy, uterine dilatation and curettage) and no family history of abnormal bleeding.

Table II. Bleeding history summary

Patient	Transfusions for postoperative hemorrhage	Family history of bleeding	Pregnancy, delivery, viable infant without hemorrhage
1	Yes	No	----
2	Yes	No	----
3	----	Yes	----
4	No	No	Yes
5	Yes	Yes	Yes
6	----	Yes	Yes

The partial thromboplastin time was abnormally prolonged in 4 of the 6 patients with hemorrhagic diathesis and was the only other screening test detecting abnormal persons. Evidence of the correctness of this demonstration is provided by the presence of further abnormalities (plasma factor defect in Patient 1, serum factor defect in Patients 2 and 3 on thromboplastin generation test study in 3 of these 4 patients). The 2 patients with serum defects also had fibrinogenopenia.



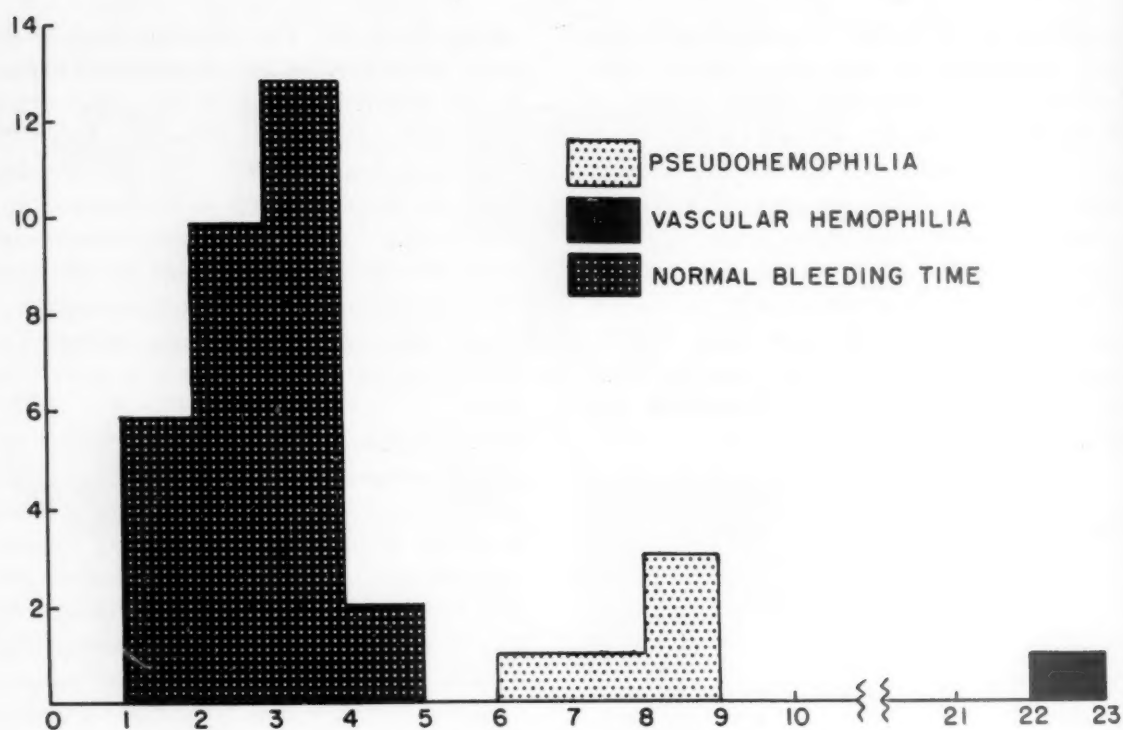


Fig. 2. Bleeding time in patients with functional uterine bleeding.

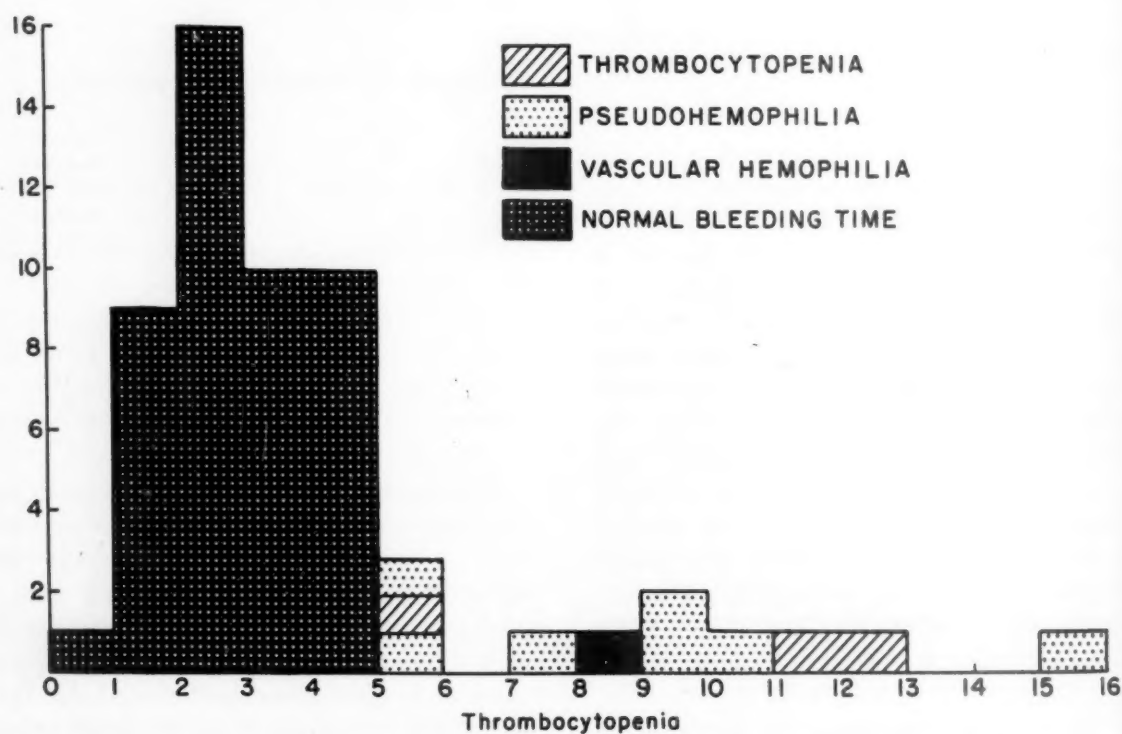


Fig. 3. Bleeding time in patients with suspected hemorrhagic diathesis—other than functional uterine bleeding.

While no abnormalities were identified in this particular series of patients by the Quick thromboplastin time, the P and P time, or by clot retraction study, the continued inclusion of these tests in a screening panel seems logical.

A further point of interest previously emphasized by others<sup>15</sup> is confirmed in this group of patients with pseudohemophilia. Three of the patients have been pregnant on one to 4 occasions each and have delivered viable infants without abnormal maternal bleeding during delivery or post partum. One patient (Patient 4) was supposed to have had an incomplete spontaneous abortion for which a curettage was done. The curettings were compatible with but not diagnostic of intrauterine pregnancy.

Diamond and Porter have recently made "a strong plea for the abandonment of routine presurgical tests of bleeding and clotting times on the basis of such evident inherent limitations as the occurrence of false-positive reactions and the fact that a normal result in no way assures a normal bleeding and clotting status in the patient."<sup>16</sup> Certainly, their point that a carefully elicited family and personal history and thorough physical examination are excellent screening procedures for identifying individuals with hemorrhagic diathesis is well taken. Furthermore, our past experience compels agreement with their view in regard to the Lee and White coagulation time. This bedside or office test has probably been responsible for more false-positive results than any other in our experience. We believe that the partial thromboplastin time assays the same information more reliably. On the merits of the bleeding time determination, however, we must differ. Perhaps it should be emphasized that special difficulty in performing bleeding time tests was encountered in the pediatric population with which Diamond and Porter were concerned.

Under the mechanics of our study, history and physical examination were completed by an independent group of exam-

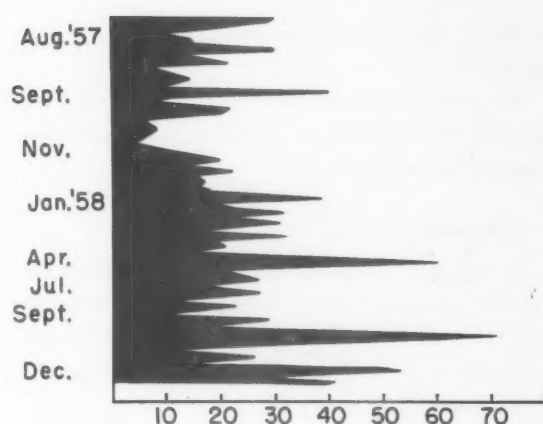


Fig. 4. Bleeding time in patients with vascular hemophilia.

iners and the screening tests performed by different personnel who were without knowledge of this first set of information. Perhaps the reproducibility and reliability was enhanced in our study by a single laboratory's performing all screening studies by standard techniques. However, in review of the charts of the patients identified as having pseudohemophilia or vascular hemophilia (pseudohemophilia plus antihemophilic globulin deficiency), studies on five occasions by the central laboratory have shown similarly abnormal bleeding times, again without our knowledge at the time our tests were performed or their beforehand knowledge of our results.

Fortunately, our patients with bleeding diathesis had already undergone diagnostic curettage or were in age groups where underlying malignant disease was not a major risk. Vaginal smears were negative for malignant cells. If carcinoma were suspected in patients with bleeding diathesis, arrangements for fresh whole blood transfusions immediately before and after operation should be made. Nelsson, Blombäck and Von Francken<sup>17</sup> have successfully administered Fraction I-O to such a patient with normalization of bleeding time and successful performance of hysterectomy. In addition, topical use of freshly mixed thrombin would help control local bleeding at the time of operation and should be used in addition to the careful tying of ligatures, though it

is imperative that this material not be injected.

Elective surgical procedures should, of course, be avoided in patients with hemorrhagic diathesis.

### Summary

Forty-three patients with functional uterine bleeding were examined. Six showed evidence of a hemorrhagic diathesis with the following findings: all had prolongation of the bleeding time; 4 had prolonged partial thromboplastin times and, of these, 3 exhibited abnormal thromboplastin generation, one demonstrating a plasma factor defect and the other 2 a serum factor defect; 2 patients had fibrinogenopenia; no abnormalities were demonstrated by the Quick time, the P and P time, or the clot retraction test.

There was a positive family history of bleeding in 3 of the patients with hemorrhagic diathesis. Three of the 4 patients undergoing surgical procedures needed transfusions to control postoperative bleed-

ing. Five of the 6 patients with hemorrhagic diathesis demonstrated either a positive family history and/or a personal need for transfusions to control postoperative bleeding.

Three (of 3) patients with hemorrhagic diathesis had normal pregnancies, delivered normal viable infants, and experienced no postpartum hemorrhage.

### Conclusions

A battery of screening tests permitted the diagnosis of previously unsuspected pseudohemophilia in 6 patients with abnormal uterine bleeding.

These patients with pseudohemophilia were able to complete pregnancy, deliver viable infants, and have uneventful recovery without abnormal bleeding.

Necessary surgical procedures should be done only when all steps have been taken to minimize the bleeding risk.

Elective operative procedures should be avoided in the patient with hemorrhagic diathesis.

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# Postmenopausal uterine bleeding of psychogenic origin

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POSTMENOPAUSAL uterine bleeding is the resumption of bleeding one or more years after the last menstrual period. In recently reported reviews, about one-third of the patients presenting with this symptom were found to have uterine carcinoma (Brewer and Miller,<sup>1</sup> 27.5 per cent; Sutherland and McBride,<sup>2</sup> 27.8 per cent; Buldain and Jacobs,<sup>3</sup> 37.7 per cent; Cope,<sup>4</sup> 34.5 per cent; Israel and Weber,<sup>5</sup> 33.5 per cent; Adamson, Brown, and Myerscough,<sup>6</sup> 28 per cent). This has emphasized the need for an immediate and thorough investigation of all cases of postmenopausal bleeding. A careful history, physical examination, cervical biopsies, cytologic smears of cervix, vaginal and endometrial aspirations, and complete curettage should be included. In instances where these procedures have not yielded the causes for the bleeding, we have also employed hysterography to demonstrate an occult endometrial polyp or submucous fibroid which might have been missed by the other diagnostic means.

There is a significant group of women with postmenopausal uterine bleeding in whom no pathologic lesion can be demonstrated, or in whom the incidental finding of a cervical erosion fails to explain adequately the active bleeding. The incidence of this group varies greatly, principally because many authors include atrophic endometrium as a benign cause of postmenopausal uterine bleeding. Atrophy is not a

cause, per se, of the bleeding, but is the normal condition of the postmenopausal endometrium.<sup>7-9</sup> Brewer and Miller<sup>1</sup> report no cause for the uterine bleeding evidenced by negative smears, negative cervical biopsies, absence of endometrial tissue, or atrophic endometrium in 38.4 per cent of their patients. Buldain and Jacobs<sup>3</sup> noted the same in 28.6 per cent and Israel and Weber<sup>5</sup> found no tissue in 49 cases, hypoplastic endometrium in 27 cases (together, 50 per cent) of 152 cases.

From Jan. 1, 1954, to Dec. 31, 1958, there were 3,129 admissions to the Gynecological Ward Service of The Mount Sinai Hospital, and of these, 2,702 patients had operations performed. Postmenopausal bleeding prompted admission to the hospital in 124 cases. Malignancy was determined in 32 patients (25.8 per cent)—corpus carcinoma in 28 and cervical carcinoma in 4. Benign pathologic conditions, to which the possible cause of bleeding could be ascribed, were found in 56 cases (45.1 per cent)—26 endometrial or endocervical polyps, 8 cervical erosions, 7 hyperplastic endometria, 4 proliferative endometria, 3 submucous fibroids, 3 pyometra, and 5 estrorrhagia. The cause of bleeding could not be determined in 37 cases (29.8 per cent). It is to this group of patients with "postmenopausal uterine bleeding etiology unknown" that we direct our attention.

In the past, many hypotheses have been advanced to explain the uterine bleeding when no obvious cause was present. The concomitant occurrence of bleeding and

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hypertension or arteriosclerosis would appear to be an obvious causal relationship. However, in the majority of cases, this correlation is lacking. An examination of the senile endometrium reveals a scanty arterial supply and total absence of the spiral arterioles so prominently displayed in functioning endometrium. In an excellent study of the endometrium and old age, Speert<sup>7</sup> considers that injury to the superficial thin-walled veins lying in proximity to expanding endometrial cystic glands may account for uterine bleeding which eluded etiological explanation. Gianaroli<sup>9</sup> has described local vascular alterations such as telangiectasia, in the senile endometrium. Probably there are many causes which cannot be discerned by our investigative techniques.

We believe that in the following 5 patients the precipitating cause for postmenopausal bleeding is psychogenic.

#### Case reports

**Case 1.** E. S., a 49-year-old married Puerto Rican woman, para 9-0-2-8, whose last normal menstrual period occurred at age 47 years, was admitted to The Mount Sinai Hospital because of bright red vaginal bleeding of 4 days' duration. She claimed that she had had an abnormal period several years previously, but thereafter had menstruated regularly until 2 years ago.

General physical examination and pelvic examination were normal. Laboratory findings were normal; Papanicolaou smears were negative. Curettage and cervical biopsies were performed which revealed small fragments of atrophic endometrium and normal cervical tissue. The patient was discharged. Three months later she was readmitted because of gushing vaginal bleeding which persisted for 5 days. Physical examination and laboratory studies were unchanged. A hystrogram was performed and no abnormalities noted. The results of a complete hematologic study were normal. Repeated cytologic smears, including endometrial aspiration, were negative.

Six years previously, at age 43 years, the patient had received a telegram from the War Department informing her that her oldest son was missing in action in Korea. Upon receipt of this information she suddenly began to bleed.

Thereafter, her periods occurred normally for 4 years. At age 47 years, coincidental with the beginning of her menopause, she received another letter stating that her son was now considered dead. She could not accept this fact. During the next 2 years, she wrote 12 letters to the War Department inquiring about him and insisting that her son was still alive. She received a tactful reply to each. When the twelfth letter was unanswered, she began to bleed vaginally, the discharge lasting for 4 days and prompting her first admission to the hospital.

She was depressed and wept when talking about her son. Since the receipt of the first telegram saying that he was missing in action her mourning had never ceased. There was extreme guilt about the role that she played in his death by signing the necessary papers which enabled him to enlist in the service at a younger age than required by law.

Abnormal uterine bleeding occurred prior to the menopause and following the menopause; both instances related to the death of her son. The defense mechanism of denial is prominently exhibited by her correspondence with the United States Government for 2 years. Upon not receiving an answer to her last letter, this mechanism of denial was rendered ineffective and she began to bleed.

**Case 2.** C. N., a 48-year-old widowed Puerto Rican woman, para 3-0-0-2, whose last normal menstrual period occurred at age 46½ years, was admitted to The Mount Sinai Hospital because of profuse vaginal bleeding of 5 days' duration. The patient had experienced hot flashes, headaches, and insomnia over the past 2 years. At age 41, she had had a unilateral oophorectomy and at age 42, she had had a vaginal plastic repair. Physical examination was normal. Laboratory findings were normal; Papanicolaou smears were negative. A hystrogram revealed a normal uterine cavity with no filling defects. Curettage and cervical biopsies revealed tiny fragments of atrophic endometrium and normal cervical mucosa.

Nine years previously the patient's husband had committed suicide. At this time she noted no depression, but thereafter developed symptoms of a peptic ulcer which continued to the present hospital admission. Shortly before this admission for postmenopausal uterine bleeding, the patient's mother became ill and died. Instead of an overt emotional reaction vaginal bleeding occurred.

**Case 3.** M. T., a 47-year-old widowed Negro woman, para 1-0-0-1, whose last normal menstrual period occurred 2½ years previously, was admitted to The Mount Sinai Hospital because of a third episode of postmenopausal uterine bleeding which lasted 7 days. In January, 1956, after 9 months of amenorrhea, she noted 4 days of vaginal bleeding, which prompted her first admission to the hospital. She had diabetes, which was controlled by diet alone. Physical examination, laboratory findings, and Papanicolaou smears were normal. Curettage and cervical biopsies were performed and revealed a small amount of tissue in early proliferative phase and normal cervical mucosa.

She was asymptomatic for 15 months, when she noted a recurrence of vaginal bleeding for 5 days. She was readmitted to the hospital, but all laboratory and physical findings were unchanged. Hysterography revealed a normal uterine cavity with no filling defects. A second curettage was performed. Again, small fragments of endometrium in an early proliferative phase were obtained.

She was discharged from the hospital and was well for 8 months. A third occurrence of postmenopausal bleeding, which lasted for 7 days, necessitated the present admission. Physical examination, laboratory findings, and Papanicolaou smears were negative. A third curettage and cervical biopsies were performed. Atrophic endometrium and normal cervical tissue were obtained.

In January, 1956, the patient had had her first episode of uterine bleeding, which coincided with the death of her divorced husband. In April, 1957, at the time of her sister's abdominal operation, the patient had had a second episode of postmenopausal bleeding. The present admission is related to concern about herself, particularly fear of uterine cancer.

**Case 4.** A. G., a 54-year-old married Puerto Rican woman, para 17-0-3-14, whose last normal menstrual period occurred 2 years previously. She was admitted to The Mount Sinai Hospital because of vaginal bleeding of 2 days' duration. The patient was well until 2 weeks prior to admission, when she noted sudden onset of moderate to profuse vaginal bleeding. She stated that she was "upset" because of the sudden hospitalization of her diabetic mother. The past history revealed that she had taken oral estrogen at irregular intervals but she denied taking any medication for the past year.

General physical examination was normal. Laboratory findings were normal except for repeated urinalyses which revealed a 2- to 3-plus glycosuria. Blood urea nitrogen was 10 mg. per cent; fasting blood sugar, 195 mg. per cent; 2 hour postprandial blood sugar, 418 mg. per cent. Papanicolaou smears were negative.

Following control of the diabetes, hysterography was performed. The uterine cavity was normal and no filling defects were noted. Cervical biopsies and curettage were performed. A few fragments of atrophic endometrium and cervical mucosa with no significant changes were obtained.

The patient spoke only Spanish and was interviewed with the help of an interpreter. She appeared childish and wore a blue ribbon in her hair. Four years previously, the patient's mother arrived from Puerto Rico and lived with her. When her mother moved away, the patient had an episode of uterine bleeding which lasted 3 days. The present episode of postmenopausal uterine bleeding began 8 days after her mother was hospitalized for diabetes at another hospital.

**Case 5.** M. I., a 66-year-old married Jewish woman, para 3-0-1-3, whose last normal menstrual period occurred at age 53, was admitted to The Mount Sinai Hospital in January, 1957, because of a third episode of postmenopausal uterine bleeding which lasted for 3 days. A summary of the 7 previous hospital admissions is given in Table I.

The present illness began 4 days prior to this admission, when she noted the sudden onset of bright vaginal bleeding which she described as a "menstrual period."

Upon admission to the hospital, general physical examination, laboratory findings, and Papanicolaou smears were negative. Hysterography revealed a normal uterine cavity. Cervical biopsies and curettage were performed. The cervical mucosa was without significant change and atrophic endometrium was obtained.

The frequent admissions to the hospital began at age 37 years, which was contemporaneous with the death of her mother. She began to feel apathetic and to lose weight. Upon the advice of a physician she became pregnant in order to cure her condition. This third pregnancy was uneventful, but the patient's condition did not improve. To the contrary, she was compelled to place the baby in a boarding home because of her inability to care for it. Following this separation, gastrointestinal symptoms appeared

Table I. Summary of previous hospital admissions (Case 5)

<i>Date of Admission</i>	<i>Age</i>	<i>Complaint</i>	<i>Diagnosis</i>	<i>Treatment</i>	<i>Findings</i>
August, 1929	37	Anorexia and rectal pain	Anxiety neurosis and hemorrhoids		
October, 1929	37	"Prolapse of rectum" and "fecal incontinence"	Hemorrhoids, severe psychoneurosis	Hemorrhoidectomy	
March, 1930	38		Severe psychoneurosis and pregnancy	Therapeutic abdominal hysterotomy and bilateral tubal ligation	
March, 1941	49		Preclimacteric menorrhagia and psychoneurosis	Curettage	
February, 1947	55		Graves' disease	Subtotal thyroidectomy	
January, 1951	59		Postmenopausal uterine bleeding	Curettage, cervical biopsies	Atrophic endometrium
January, 1955	63		Postmenopausal uterine bleeding	Curettage, cervical biopsies	Atrophic endometrium

and necessitated the first admission to The Mount Sinai Hospital. Her complaints included indigestion, diarrhea, fecal incontinence, prolapse of the rectum, constipation, loss of weight, anorexia, nausea, epigastric pain, and the finding of food particles in her stool. It is interesting to note that the patient's mother had died of gastric cancer and that the patient's symptoms were entirely in this sphere. At the time of her third admission to the hospital the symptoms of depression and gastrointestinal difficulties gradually fused. At this time, the patient was indifferent to food and her surroundings. She was a withdrawn, self-absorbed, passive, complaining woman whose only way of asserting herself was by suffering, becoming ill, and being unhappy.

The mechanism of bleeding as her avenue for discharge of tensions started at the age of 8 years. At that time, the birth of a younger brother and the threats inherent in this were allayed by the intermittent occurrence of nose bleeds over a 4 year period. With the onset of the menarche, the nose bleeds stopped. The episodes of abnormal bleeding, before and after the menopause, may be thought of as a means by which her body discharged tensions, specifically, as a

means to cope with a depression following her mother's death.

### Comment

The literature on postmenopausal uterine bleeding of psychogenic origin is scant. Blaikley<sup>10</sup> described a 58-year-old woman 2 years postmenopausal who had consulted him because of continued bleeding following a curettage. No evidence of carcinoma in the curettings was reported. She had had recurrent vaginal bleeding, which Blaikley stated in each instance occurred on the day which marked either the birth or death of one of 3 sons, all of whom had been killed during World War II. Stieve<sup>11</sup> described a 47-year-old woman who was 7 years postmenopausal. The patient had received notification of the death of her husband who had been a prisoner of war for 5 years. Shortly thereafter, she began to have uterine bleeding. She consulted her physician who suggested a more detailed examination to rule out the possibility of uterine cancer.



Fourteen hours after the onset of bleeding, the woman hanged herself, partly because of grief over her husband's death and partly out of fear of cancer. An autopsy was performed, and the complete pathologic examination revealed that there were no abnormalities of the ovaries or uterus; in fact, the uterine mucosa was atrophic. This is a significant report because it is the only instance where a complete histologic study of the uterus and ovaries was made in a patient with postmenopausal uterine bleeding apparently due to psychological causes.

Analyses of these 2 cases from the literature and of our own cases suggest a common precipitating etiological cause. The uterine bleeding is associated with the death of a person considered important by the patient.

Our investigation of the psychogenic factors in postmenopausal uterine bleeding was the result of observations made in women with functional uterine bleeding.<sup>11-14</sup> The psychological mechanism leading to uterine bleeding has been described elsewhere.<sup>12-14</sup> In essence, it was found that instead of manifesting grief or depression over the loss of a loved one some women exhibited a somatic equivalent in the form of uterine bleeding. For this reason, uterine bleeding following the loss of a loved one has been called "the weeping of the mourning womb."

During the reproductive era, a commonly utilized and easily recognized compensatory mechanism for the loss of a loved one is to become pregnant. After the menopause, this modus operandi is no longer available.

Case 5 illustrates a patient's attempt to cope with depression, following the death of her mother, by having a child. Many years later, other episodes of depression were manifested by uterine bleeding.

As a result of the intensive educational programs for early signs of cancer, all patients associate unexpected or unusual bleeding with uterine carcinoma. It is mandatory that a complete investigation be performed; however, it is also important to note that these patients are fundamentally depressed. Stieves' case and our cases are examples. The absence of pathologic findings to explain the postmenopausal uterine bleeding, in conjunction with observations illustrated in our case histories, permits the gynecologist to direct his attention to the concealed depression. Reassurance will be adequate in most instances, but where the depression is too deep, psychiatric help is indicated.

### Summary

1. Five cases of postmenopausal uterine bleeding are presented. Gynecologic examination and findings did not explain the bleeding.

2. In these instances and in 2 observations found in the literature, bleeding followed loss of, or separation from, a loved one.

3. These observations confirm an earlier observation made regarding certain cases of functional uterine bleeding; i.e., this bleeding is a somatic equivalent of the psychological reaction of depression.

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# Habitual premenstrual spotting following electrocauterization of the cervix: a newly observed phenomenon

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IN 1943 a woman was seen with chronic cervicitis for which an electrocauterization of the cervix was done. Three years later the patient returned saying that for the past year she had noticed a scant brown vaginal discharge for 7 days preceding each menstrual period. Since that occasion, the complaint of premenstrual spotting following cauterization has been forced upon my attention by many women. In the past 12 years over 200 such cases have been seen.

Few persons do not know that bleeding from any body orifice may be a sign of cancer, therefore it is not surprising that a woman with this repeated spotting becomes alarmed. It would therefore seem important that the physician become familiar with this phenomenon in order that he can differentiate it from other causes of premenstrual bleeding. These include submucous myoma of the uterus and cervical or endometrial polyp, as well as malignancy of the cervix or fundus. Differential diagnosis makes accurate treatment possible and will avoid unnecessary operations.

## Material

The material for this study consists of 201 cases of premenstrual spotting, 11 of which followed electroconization and 190 electrocauterization. These have been collected over a period of 12 years and the majority

have been followed for 5 years or longer. The cauterization was done in most cases by myself, but 59 of the women had had the treatment done by one of 56 other physicians.

## Occurrence

In order to discover the percentage of patients developing premenstrual spotting, a follow-up was attempted on all patients cauterized by me from 1949 through 1951. There were 200 of these and in June, 1954, 153 could be traced. Forty-eight or 32 per cent had developed the characteristic spotting. The eventual incidence might well be somewhat higher as this group had been followed only 3 to 5 years, and the interval between cauterization and the time at which the patient first notices the bleeding is sometimes longer than this.

At the time this condition was first observed, I was concluding each cauterization by placing the cautery tip about one half inch within the cervical canal and applying the current briefly while pressure was made for a moment at 12, 3, 6, and 9 o'clock. It was thought that this treatment of the canal might be responsible for the spotting that followed. In the past several years cauterization has been confined to the portio and the external os. This change has not affected the efficiency of cauterization as a treatment of chronic cervicitis; neither has it decreased the incidence of premenstrual spotting that follows.

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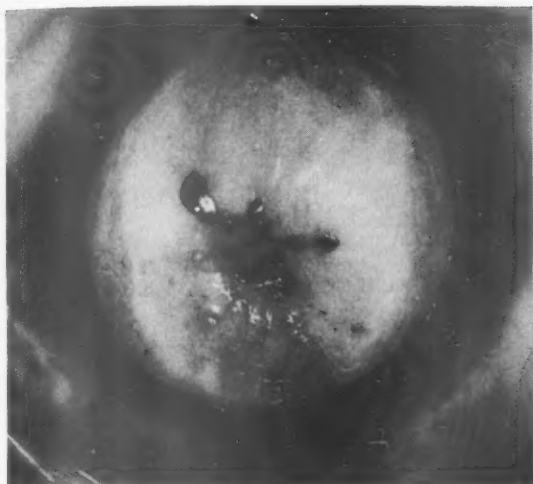


Fig. 1. Blebs on cervix following electrocauterization done 3 years previously. Spotting had occurred one to 2 days before each period, beginning 3 months after cauterization. Photograph taken 2 hours after spotting was noticed. Cervix wiped clean to show lesion clearly.



Fig. 2. Circular lesion following cauterization done 15 months previously. Photograph taken on twenty-first day of cycle and before spotting had begun for that month. Photomicrograph of this lesion is shown in Fig. 4.

There is a remarkable variation in the time interval between cauterization and the first occasion on which spotting is observed by the patient. Occasionally, bleeding is noticed preceding the second menstrual period after the cauterization. In one case it did not show itself, or at least was not noticed by the patient, until 16 years after the treatment. In a majority of the cases it is discovered within the first year, in many within 2 to 5 years, and in a few, after 5 years.

### Symptoms

The premenstrual spotting follows a distinct pattern. It begins from one to 7 days before the onset of menstruation proper and continues until the flow starts. In color it is a dirty brown—neither pink nor red. There is not enough bleeding to make a pad necessary unless the woman is overly fastidious. It is usually noticed only on the toilet paper; when it does soil the clothes it is likely to appear as a brown smear rather than a spot. Although scant, it may be unpleasant and annoying to the woman. She often describes the condition by saying, "Now it takes my period two or three days to get started." This bleeding is not seen at odd

times during the month or following coitus. No pain, odor, or irritation accompanies the discharge.

### Description of lesion

The lesion from which this scant bleeding comes each month is most prominent shortly before the onset of spotting. At that time it is a small, dark red, slightly raised bleb or bar. There are usually 2 or 3 such lesions on a cervix and they appear against a clean, pink portio (Figs. 1 and 2). The blebs develop between the radiating strokes made by the cautery or at the distal ends of these strokes. In the latter case the lesion may take the form of an arc or an almost complete circle about the cauterized area (Fig. 2). A cervix bearing such blebs is a familiar sight to a gynecologist, who on seeing it would know immediately that the patient had once had a cauterization. At midmonth the lesion is flat, less sharply defined, and easily overlooked.

When inspection is carried out after spotting has begun, a minute amount of bright pink or red blood can be seen coming from one or more of the lesions. This ooze can best be demonstrated by gently cleaning the cervix with cotton, waiting a few seconds,



Fig. 3. This patient had been spotting 48 hours. Cervix and speculum are soiled with the characteristic dark brown blobs of old blood.

and then touching a bleb with a cotton applicator. When the applicator is removed blood can be seen on its tip. In addition to the ooze from the lesions, there is often, but not always, a very small amount of blood from the os. If the bleeding has been going on for several hours small blobs and strings of brown pastelike material will be seen on the cervix and in the vaginal vault (Fig. 3). The bleeding is so scant that by the time enough has accumulated to drain from the vagina and so attract the patient's attention, the bright red of oxyhemoglobin of the fresh blood has been reduced by the acid of the vagina to the dark brown which the woman sees. This explains why she always describes the discharge as brown or "black" rather than the pink or red of fresh blood.

The microscopic picture of the lesion shows more variation than the gross. This is not surprising since biopsy was done from one month to 9 years following cauterization and specimens were taken at all phases of the menstrual cycle. In all specimens the lesion is covered by squamous epithelium which shows no papillae. The epithelium is considerably thinner than that seen covering the adjacent normal cervical tissue and, in some cases, it has undergone a cystic degeneration. When biopsy is done after spotting has begun some sections show

the break in the epithelium from which the blood is escaping. All specimens show some degree of increased vascularity and extrusion of blood into the tissue beneath the epithelium (Fig. 4). If the biopsy is done during the premenstrual or menstrual phase the blood is fresh. If taken at other times during the cycle there is degeneration of the red cells and in old lesions brown blood pigment (hemosiderin) is present. In these latter cases phagocytic endothelial leukocytes containing pigment granules can sometimes be seen. The slides suggest that, as in normal menstruation from uterine endometrium, the blood leaves the vessels in one of two ways: by actual break in the wall of an arteriole or capillary or by diapedesis through the wall of a capillary.<sup>1</sup>

One of the most characteristic and interesting aspects of the lesion is a lacy appearance of the stroma (Figs. 4 and 5). This is due to edema of the tissue and seems to appear at the margins of the involved area. The spindle connective tissue cells of the cervix are widely separated by a faint pink-staining material. Sections prepared with connective tissue stain show that this is not connective tissue matrix. The cause of the edema is not known. It is not due to general premenstrual swelling as specimens taken early in the cycle show the same picture. It is thought that the edema may be tissue reaction to extravasated blood.

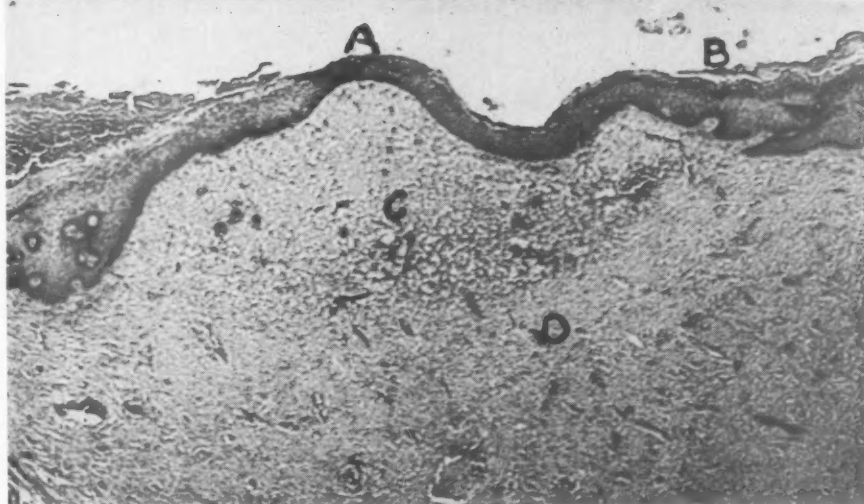
Biopsy was done in over 80 of these lesions of the cervix. However, early specimens were taken with a punch biopsy and the tissue was so distorted that little could be learned from it. More recent specimens have been taken by removing a considerable wedge of tissue with a knife. Good material has been available for study in 40 cases.

Eleven of these biopsies showed frank endometriosis (Fig. 6). All of these included both glandular and stromal elements, although in a few only one or two glands were present and in one case only fragments of a gland. With the exception of one case encountered recently, all slides suggesting endometriosis were examined by Dr. Emil Novak in January, 1956, and diagnosed cer-





4



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Fig. 4. Lesion of cervix following electrocauterization. Biopsy done on twenty-fourth day of cycle. Bleeding had not yet occurred but extravasated fresh blood can be seen in edematous tissue under the still intact epithelium. ( $\times 280$ .)

Fig. 5. Typical lesion of cervix following electrocauterization. Biopsy done on twenty-sixth day of cycle and before onset of premenstrual spotting. A, Thinned epithelium; B, edge of lesion showing epithelium of usual thickness with papillae; C, edematous area; D, normal-appearing compact cervical tissue. ( $\times 280$ .)

vical endometriosis. In 3 of these patients there was clinical evidence of additional areas of endometriosis within the pelvis, but in none was there any suggestion of direct extension to the cervical lesion. In addition to the 11 cases of conventional endometriosis of the cervix there were 2 specimens with

stromal changes which warranted the diagnosis of stromal endometriosis. Clinically the lesions showing endometriosis spot in exactly the same manner as those in which no glands nor endometrial stroma is found.

One of the most interesting cases of the series was that in which a portion of the



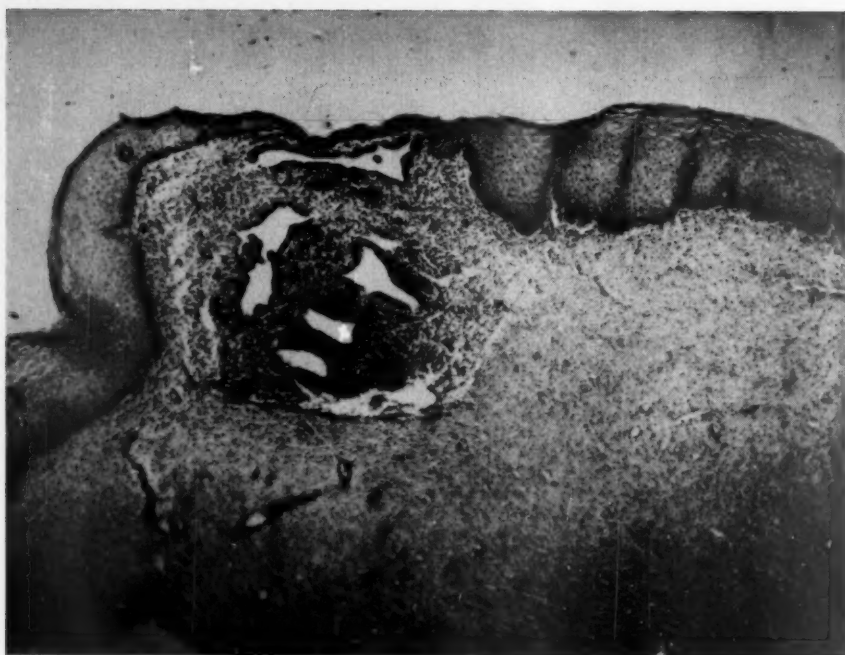


Fig. 6. Small bleb which showed endometriosis. Biopsy done on twenty-first day of cycle. Grossly such a lesion cannot be distinguished from blebs which are not endometriosis. ( $\times 280$ .)

lesion showed microscopically the typical picture of thinned epithelium, increased vascularity, and edema. Adjacent sections show this picture merging gradually into one of frank endometriosis (Figs. 7 and 8). This suggests that had it been practical to do serial sections on all specimens more cases of endometriosis might have been found.

#### Associated pathologic conditions

Could the presence of some associated pathologic condition such as a myoma or a uterine polyp be responsible for this bleeding? Associated pathology was diagnosed in 19 of the cases. In 15 a small intramural myoma was felt on pelvic examination. Only 4 of the 19 cases came to operation. Two of these showed an intramural myoma, one a myoma of the broad ligament and one a nonmalignant cyst of the ovary. This incidence of accompanying pathologic conditions does not seem high and it is felt that it could not have been a significant factor in producing the spotting that was observed in the total group.

#### Course

When no treatment is given, the bleeding may stop spontaneously after a few months or it may continue for many years. In about one third of the cases the woman notices no further bleeding after the first year. In many it continues for from 2 to 5 years. One woman was annoyed with the discharge for 12 years. It gradually disappeared when she approached menopause. Pregnancy seems to cure the condition. In no case in which the woman has become pregnant has the bleeding returned with the resumption of menstruation after delivery. A majority of the cases in this series have been followed for 5 years or longer. In none of the women has uterine carcinoma developed.

#### Diagnosis

A bloody vaginal discharge always requires meticulous investigation. In each case it should include a careful history and vaginal examination, inspection of the cervix at the time of the bleeding, a Papanicolaou

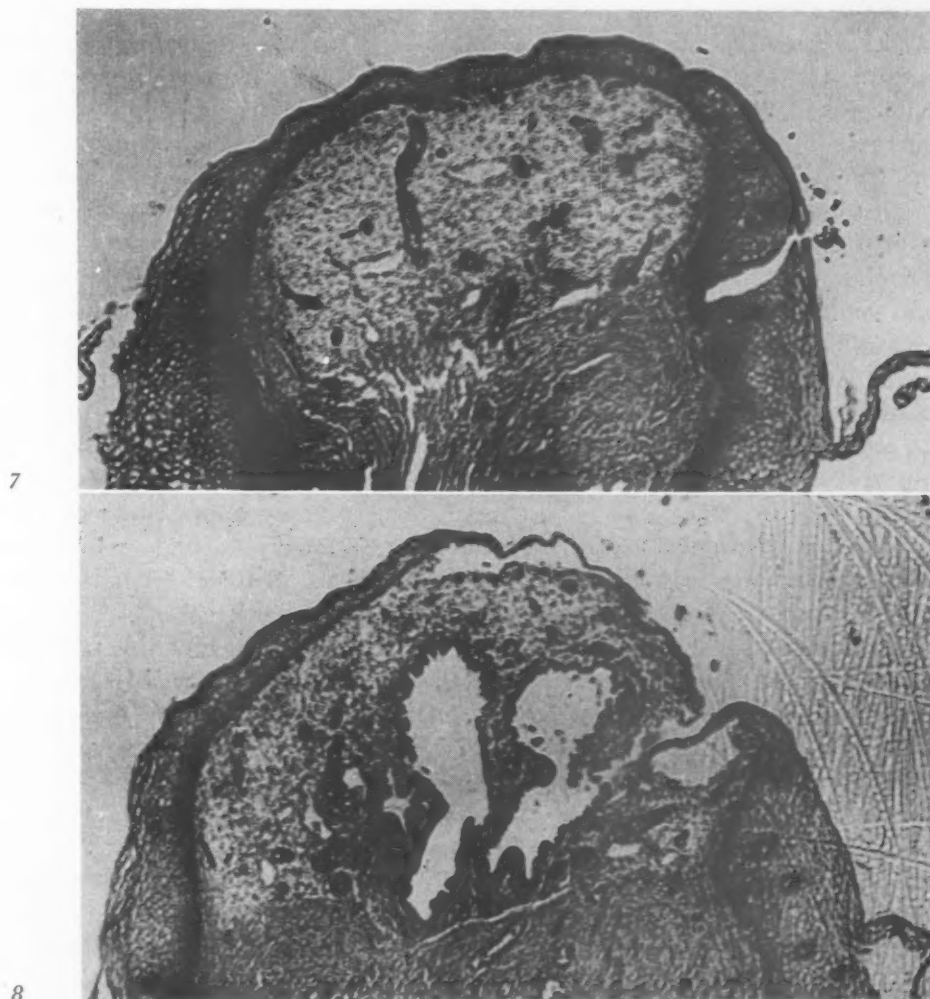
smear and, if indicated, a cervical biopsy. A diagnostic curettage is seldom, if ever, necessary.

### Treatment

Chemical cauterization of the cervical os and canal, repeating the original electrocauterization and taking care to destroy all portio lesions, dilatation and curettage of the canal, and electroconization of the cervix have all been used as treatment of this condition without success. The only effective treatment has been conization of the cervix with a knife. This is easily done in the hospital, of course, but, as the conization need

not be deep, it can also be done in the office. A knife or a punch biopsy is used to remove any portio lesions present and also the superficial tissue about the os. A small cone extending up into the canal for about one half inch is then removed with the knife. Bleeding is controlled by a narrow gauze pack in the canal and a vaginal pack against the cervix. No treatment is necessary in those patients who do not find the discharge annoying. In every case, however, the woman should have an explanation of the cause of bleeding and adequate reassurance.

Neither curettage nor major pelvic operation is indicated in this condition but judg-



**Figs. 7 and 8.** Sections from identical bleb. Biopsy done after onset of spotting (see break in epithelium in Fig. 8) but 24 hours before menstruation began. Fig. 7 shows margin of bleb with picture characteristic of the lesion of this study. Fig. 8 taken a few sections near center of lesion but from same fragment shows distinct endometriosis. ( $\times 280$ .)

ing from histories of the women in this series both are being resorted to rather frequently through lack of knowledge of the phenomenon.

### Comment

Three interesting questions arise in regard to this condition: (1) what causes the bleb to form, (2) why does it bleed premenstrually, and (3) what is its relationship to cervical endometriosis? This study does not give a satisfactory answer to any one of these questions but does establish a few additional facts which may be pertinent.

The lesion apparently forms only in the presence of infection of the cervix. Cauterization is done for chronic cervicitis so that in these cases this condition was invariably present. In 21 cases in which the cervix was unblemished (all nulliparas and some virgins) a "T" was cauterized on the anterior lip. These women have been followed for a minimum of 18 months. None has developed a bleb and none has shown any spotting. The burn on a clean cervix heals quickly and completely so that in a few weeks it is impossible to tell that cauterization was done. To produce a bleb an infected cervix must be traumatized and the trauma must be in the form of a burn as the spot does not appear following biopsy nor knife conization.

Why does the lesion of this study bleed? At one period it was thought that a general premenstrual congestion of the pelvis might well cause spotting. However, this seems unlikely since large areas of chronic cervicitis and granular lesions of the cervix do not have this rhythmic bleeding. There are 3 elements in the development of an area of endometriosis: the appearance of endometrial glands, characteristic changes in the stroma and a change in blood vessels of the involved area that makes them susceptible to hormonal influence. These changes do not always develop simultaneously nor are all 3 necessary for a diagnosis of endometriosis.<sup>2</sup> Could it be that the trauma of the burn in an infected field produces a change which in a few cases proceeds to frank endometrio-

sis or stromal endometriosis, but in many more produces only a change in the blood vessels which causes them to respond to hormonal stimulation by rhythmic bleeding?

Regarding the cases of conventional endometriosis of the cervix in this series, it is interesting to recall that they have all developed in areas of previous chronic cervicitis which, as is well known, are covered with columnar epithelium which has probably grown down from the endocervix. This columnar epithelium of the endocervix is closely related to endometrium by way of their common origin from the celomic epithelium of the embryo. This fact would make metaplasia in this condition at least theoretically tenable.

It is likely that endometriosis of the cervix as well as endometriosis in other areas has a multiple histogenesis. The cases of endometriosis in this series could have been produced by implantation. Cauterization was done in most instances shortly after a menstrual period but the mucosa is not intact by the onset of the next period and there would be opportunity for implantation. In this connection it is interesting to note that Williams,<sup>3</sup> in a series of 35 cases of cervical endometriosis, found that 13 had been preceded by cauterization. On the other hand, Thomas,<sup>4, 5</sup> in over 35 cases of conization of the infected cervix by use of a biopsy punch, did not observe the development of a single case of cervical endometriosis. Neither did he see the phenomenon of premenstrual spotting nor the development of the bleb of this study. The nature of the trauma (burn of cautery as against cut of biopsy forceps) certainly plays a part in producing the lesion of this study and perhaps in producing cervical endometriosis as well.

### Summary and conclusions

1. Of 153 patients who underwent electrocauterization and who were followed for from 3 to 5 years, about one third developed a characteristic premenstrual spotting.

2. Because of the association of vaginal bleeding with uterine cancer such spotting may cause the patient great anxiety. It

would seem important that the physician become familiar with this phenomenon so that he can differentiate it from the more serious causes of vaginal bleeding. Having done this he can reassure his patient and can avoid unnecessary operations.

3. Two hundred and one women with this condition were studied. The premenstrual spotting develops from one month to several years following the cauterization. It occurs from one to 7 days preceding each period, is a dirty brown in color, and is too scant to require a pad.

4. The condition may disappear spontaneously after a few months or may persist for many years.

5. The bleeding comes as an ooze from small cherry-red streaks or blebs which appear on the portio of the cervix.

6. These lesions show a characteristic mi-

croscopic picture of edema of the stroma, thinning of the overlying stratified epithelium, and extrusion of blood into the area. Eleven cases of frank cervical endometriosis and 3 of stromal endometriosis appeared in the group.

7. Effective treatment consists of surgical removal with knife or biopsy punch of the portio blebs and of the tissue about and just within the external os.

8. The question of fundamental etiology, of cause of the rhythmic bleeding, and of the relationship of the lesion to cervical endometriosis cannot be satisfactorily answered by this study.

9. All unusual vaginal bleeding calls for meticulous investigation, but this phenomenon of premenstrual vaginal spotting following cauterization can be as easily and as definitely recognized as can ovulation bleeding.

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# Primary carcinoma of the Fallopian tube

With report of 12 new cases

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AMONG the cancers of the female reproductive system, primary carcinoma of the Fallopian tube is comparatively rare, but it does occur with sufficient frequency to create a difficult diagnostic problem, an unsatisfactory therapeutic situation and an interesting pathological study. Of importance is the fact that the clinical diagnosis is rarely made, and only 3 or 4 instances of preoperative recognition have been noted in the literature. The descriptions by Raymond<sup>1</sup> in 1847 and later by Rokitansky<sup>1</sup> in 1861 have been accepted as probably the earliest recognition of the existence of this lesion, but for the first comprehensive discussion of this malignancy the majority of authors acknowledge the work of Orthmann<sup>2</sup> in 1888. Approximately 449 cases were reported in a thorough review of the literature by Mitchell and Mohler<sup>3</sup> in 1945, and a further search of the literature to date revealed the existence of approximately 663 established cases. As shown in Table I, the incidence of primary carcinoma of the Fallopian tube among genital tract cancers reported from other institutions ranged from 0.16 per cent to 1.16 per cent.

At the Chicago Lying-in Hospital from May, 1931, to January, 1957, 12 cases of primary carcinoma of the Fallopian tube, including one case of carcinoma in situ, were

diagnosed, which represented an incidence of 1.1 per cent among 1,087 primary genital tract carcinomas. The cases in this series were carefully evaluated and met the following criteria:

1. **Gross examination.** The main tumor was within the tube. When the ovaries and uterus were involved by a malignant lesion, its size and distribution were characteristic of metastasis.

2. **Microscopic examination.** The mucosa was replaced in whole or in part by an adenocarcinoma which showed histological characteristics of the endosalpinx. When the ovaries and uterus were involved by a malignant lesion, its size, distribution, and histological similarities resembled a metastatic process.

Eleven of the 12 lesions were unilateral, 5 on the right and 6 on the left. One carcinoma was bilateral. Carcinoma in situ<sup>4</sup> of the tube was diagnosed in one of this group.

## Clinical data

The clinical aspects of this series failed to establish any similarity of pattern. The average age was approximately 48 years, with a range from 35 to 60 years. Fullerton<sup>5</sup> reported the oldest patient, 80 years, and 3 cases<sup>6, 7</sup> have been recorded in 18-year-old women. All 12 were married and 11 of the 12 were white.

Six of the patients had had no term pregnancies but one had had 3 spontaneous abortions. Of the others, 2 had had one term pregnancy, one had had 2, and the other 3

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Table I. Incidence of carcinoma of the Fallopian tube

Author	Institution	Years covered	Gynecological admissions	Gynecological malignancies	Cases	%
Weckes, Anz and Whiting <sup>12</sup>	Queen of Angel	10		640	7	1.09
Hu, Taymor, and Hertig <sup>11</sup>	Free Hospital	45	90,611	3,878	12	0.31
Lofgren <sup>9</sup>	Mayo	40		10,000	16	0.16
Finn and Javert <sup>10</sup>	Woman's N.Y.C.	16	20,617	952	5	0.50
Fullerton <sup>5</sup>	Cleveland	13	22,330		4	
Mitchell and Mohler <sup>8</sup>	Philadelphia	47	(6,747 salpingectomies)		1	
Emge <sup>13</sup>	Standford Lane			1,350	5	0.49
Frankel <sup>15</sup>	Beth Israel	10		435	7	1.60
	Harlem Hospital	10		687	3	0.43
Hayden and Potter	Chicago Lying-in	26		1,087	12	1.10

had had 3 or more term pregnancies. Many authors<sup>11, 14</sup> stress the frequent association of sterility with primary carcinoma of the tube. The 50 per cent incidence in this series was high, but it was important to note that in the 6 nulliparous women there was evidence of chronic salpingitis, which undoubtedly was the major contributing factor in the infertility and possibly even a predisposing factor in the development of the carcinoma.

Six of the patients were postmenopausal and 4 of these 6 patients presented the initial complaint of vaginal bleeding with an

average duration of 6 weeks. The fifth patient complained only of a vague abdominal distention and pain, and the sixth patient was without gynecological complaints. Of the 6 women within the reproductive age, 2 were without gynecological complaints, 2 complained of metrorrhagia, and the other 2 complained of abdominal pain.

In 1915 Latzko<sup>8</sup> described a syndrome, hydrops tubae profluens, which was characterized by the relief of pain and the disappearance of a tumor following a profuse vaginal discharge, and which he considered

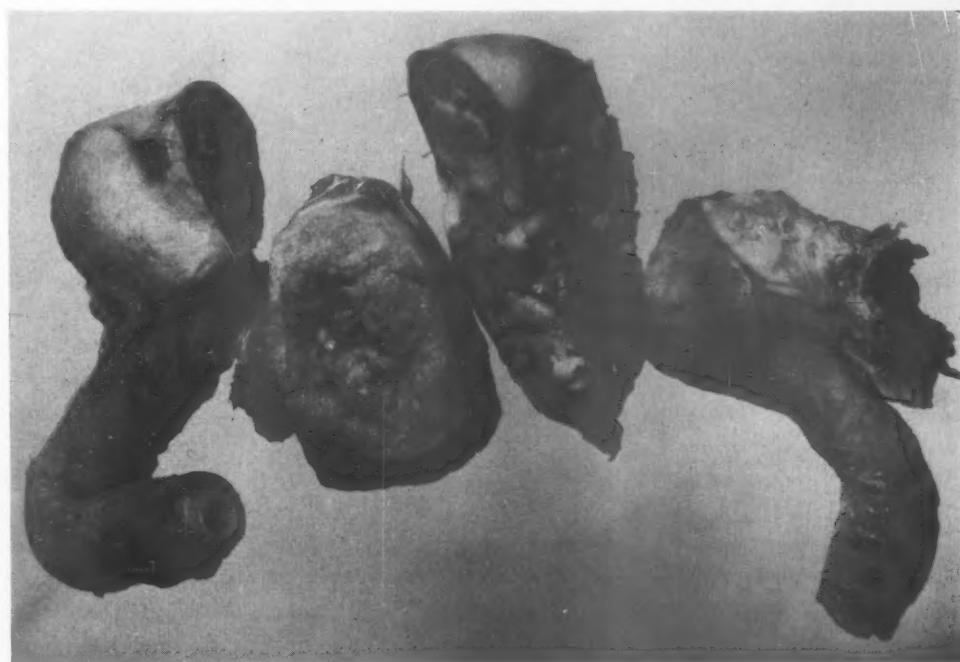
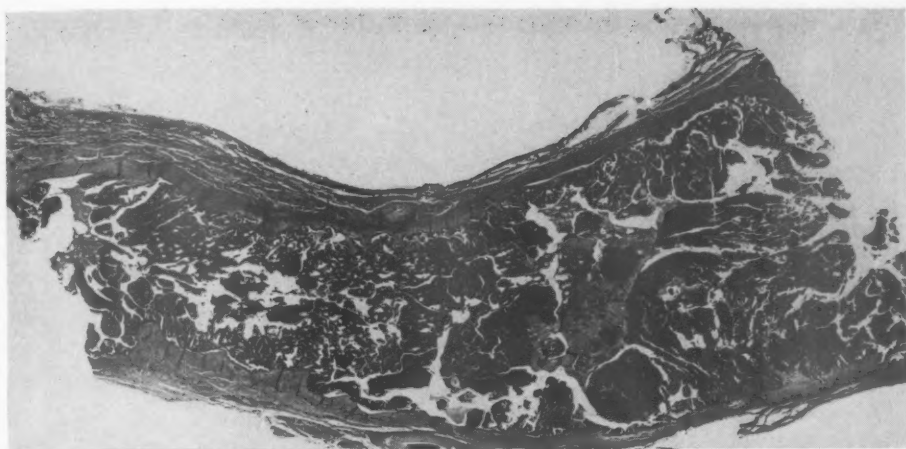


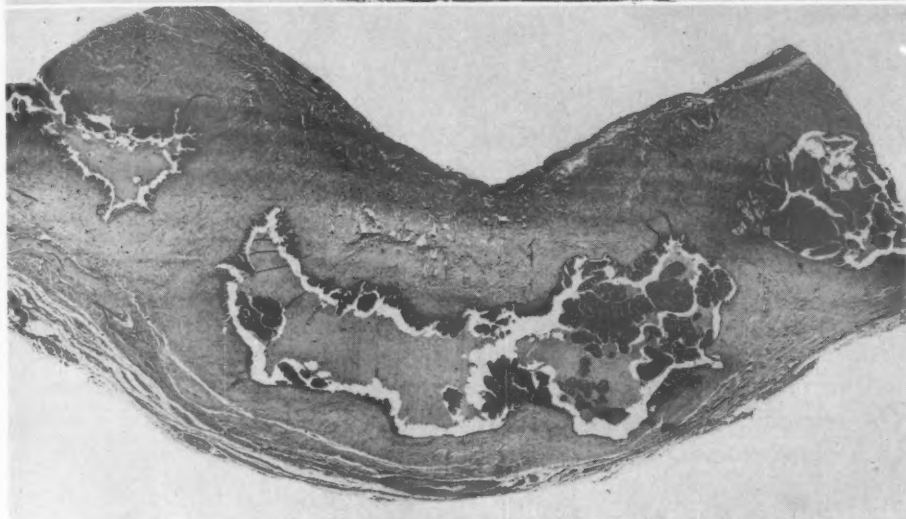
Fig. 1. Bilateral primary carcinoma of the Fallopian tube, gross specimen.

Table II. Summary of clinical data on 12 cases of carcinoma of the Fallopian tube

	Initial complaint, duration	Preoperative pelvic examination	Preoperative diagnosis	Treatment	Survival
L. T. 23352	Postmenopausal bleeding (12 weeks)	Left cystic mass in cul-de-sac	Ventral hernia; ovarian cyst	Subtotal hysterectomy; bilateral salpingo- oophorectomy; postoperative radium (1,200 mg. hr.); x-ray therapy	3 years; died; carcino- matosis
B. A. 55727	Vaginal bleeding, abdominal distention (3 weeks)	10 cm. left adnexal mass in cul-de-sac	Ovarian cyst	Left salpingectomy; x-ray therapy; post- irradiation hysterectomy; right salpingec- tomy; bilateral oophorectomy	2 years; died; carcino- matosis
L. C. 110282	Postmenopausal bleeding (1 week)	Corpus size of 12 weeks' preg- nancy; right ad- nexal mass; normal cervix	Myomas	Subtotal hysterectomy; bilateral salpingo- oophorectomy; x-ray therapy	18 years; no recurrence
R. B. 138747	Right lower quadrant pain (12 weeks), hemorrhoids	Bilateral tender adnexa; nodular irregularity in cul-de-sac	Endometriosis; regional enteritis	Appendectomy; bilateral salpingo-oophorec- tomy; x-ray therapy	4 years; died; carcino- matosis; bowel ob- struction
C. D. 148774	Distention, pain in left lower quadrant, pain down leg (24 weeks)	Irregular corpus size of 10-12 weeks' preg- nancy	Multiple myomas	Hysterectomy; bilateral salpingo-oophorec- tomy; x-ray therapy	7 years; no recurrence
A. O. 377270	Postmenopausal bleeding (5 weeks), fatigue	Corpus irregularly enlarged	Myomas	Subtotal hysterectomy; bilateral salpingo- oophorectomy; x-ray therapy	12 years; no recurrence
R. H. 66121	Postmenopausal bleeding (ovarian cyst) (6 weeks)	Right adnexal mass in cul-de-sac, 10 cm.	Ovarian cyst	Hysterectomy; bilateral salpingo-oophorec- tomy; x-ray therapy	4 years; died; carcino- matosis
L. R. 468371	Pelvic mass; no complaint; regular (24 weeks)	Corpus irregularly en- larged to size of 10 weeks' pregnancy	Myomas	Hysterectomy; bilateral salpingo-oophorec- tomy; x-ray therapy	1 year; died; carcinoma- tosis
M. B. 519183	Soreness in rectum (3 weeks)	Corpus irregularly size of 12-14 weeks' pregnancy; bilateral adnexal masses	Myomas; pelvic inflammatory disease	Hysterectomy; bilateral salpingo-oophorec- tomy	2 years; died; carcino- matosis
R. H. 571213	Vaginal bleeding; left lower quadrant pain (4 months)	15 cm. irregular right adnexal mass	Ovarian neoplasm	Hysterectomy; bilateral salpingo-oophorec- tomy; x-ray therapy	15 months; died; car- cinomatosis
M. P. 607172	Urological complaints (2 months)	10-12 cm. cul-de-sac mass	Ovarian tumor	Bilateral salpingo-oophorectomy (previous vaginal hysterectomy); x-ray therapy	1 year; died; carcino- tosis
S. S. 577372	Dysmenorrhea; pelvic inflam- matory disease	Corpus enlarged; bilat- eral adnexal masses	Pelvic inflamma- tory disease, myomas	Hysterectomy; bilateral salpingo-oophorec- tomy; appendectomy	24 months; living



2



3

Fig. 2. One Fallopian tube opened longitudinally and showing involvement of all surfaces with carcinoma. ( $\times 6$ ; reduced  $\frac{1}{4}$ .)

Fig. 3. Opposite Fallopian tube opened longitudinally and showing involvement of all surfaces with a primary carcinoma. ( $\times 6$ ; reduced  $\frac{1}{4}$ .)

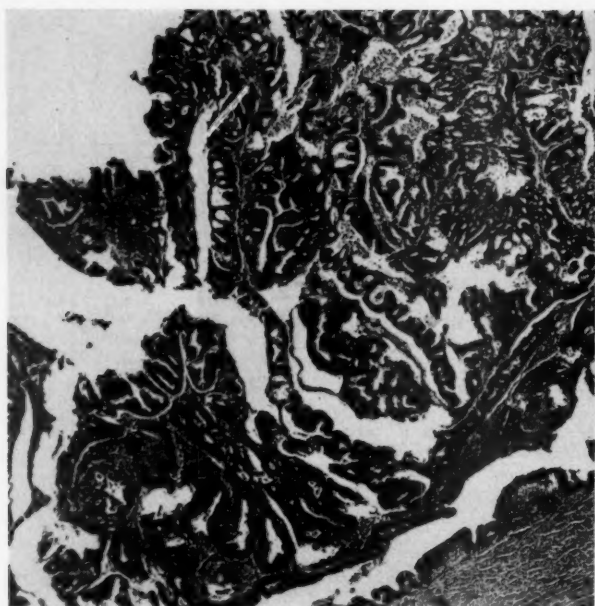
indicative of tubal malignancy. However, this syndrome was not present in this series. Among the entire group, as shown in Table II, 6 of the 12 patients had an initial complaint of vaginal bleeding. Three patients had pain and 3 patients were without specific gynecological complaints. The insidiousness of the process is emphasized by the fact that all 12 patients at the time of the initial examination had a definite palpable mass but the actual diagnosis was not suspected in a single case. The lack of characteristic history or physical findings and the frequent association of other pelvic conditions made the clinical recognition almost impossible. The preoperative diagnosis included multiple myomas, pelvic inflamma-

tory disease, endometriosis, and ovarian neoplasm. Ascites was not found in any of the cases although it had been reported by others as a frequent associated finding.

#### Pathological description

The gross descriptions were available in all the cases and they were sufficiently detailed for accurate evaluation. In the instance of the bilateral primary carcinoma, externally the process appeared as a bilateral hydrosalpinx (Fig. 1) but when the tubes were opened the malignancy was found to involve the lumen of the entire length of both Fallopian tubes (Figs. 2 and 3). The external description in 7 cases considered the process as a cystic inflammatory





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Fig. 4. Primary carcinoma of the Fallopian tube, papillary-type adenocarcinoma. ( $\times 50$ ; reduced  $\frac{1}{3}$ .)



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Fig. 5. Primary carcinoma of the Fallopian tube showing typical papillary-alveolar type adenocarcinoma. ( $\times 50$ ; reduced  $\frac{1}{3}$ .)

adnexal mass with dense adhesions, but in 3 instances gray friable nodules involving the fimbriated ends were described as probably metastatic lesions. The remaining specimen was considered to be a hematosalpinx and the cross section revealed the carcinomatous lesion.

In all specimens there were associated benign lesions. Multiple myomas were found in 7 specimens, endometriosis or adenomyosis was found in 5 instances, and a benign ovarian cyst was found in one instance. In 11 specimens there was either gross or microscopic evidence of chronic salpingitis.

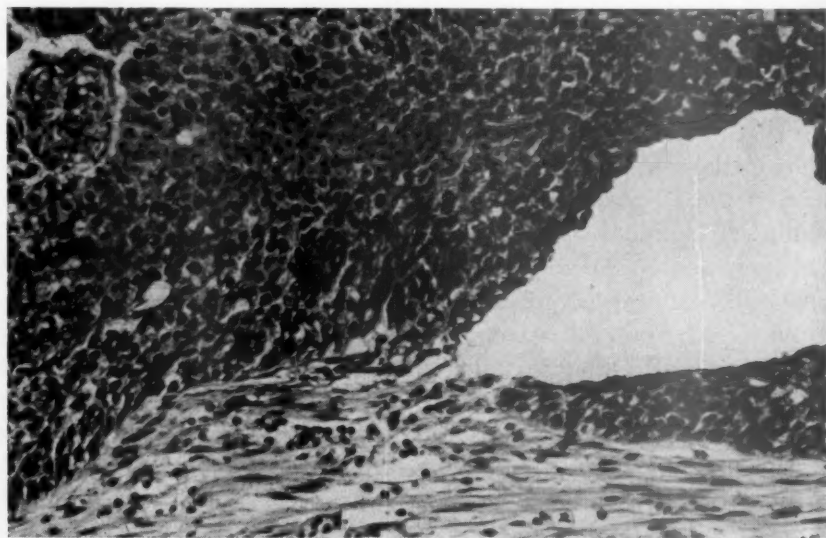


Fig. 6. Papillary-alveolar adenocarcinoma showing highly anaplastic cells and slight attempt at gland formation. ( $\times 250$ ; reduced  $\frac{1}{4}$ .)

No correlation could be established between the microscopic pattern of the adenocarcinoma and the prognosis, as was reported by Hu, Taymor, and Hertig.<sup>11</sup> It is of interest to note that the more accepted classification of papillary and papillary-alveolar adenocarcinomas by Sanger and Barth<sup>14</sup> was applicable, but in every instance gradations or combinations of the patterns could be demonstrated. In 2, the pattern was essentially the papillary type (Figs. 4 and 5); in 6, a mixture of the papillary and the more solid papillary-alveolar adenocarcinoma; and in the other 3 a typical papillary-alveolar pattern was the predominant type (Fig. 6). In the case of the bilateral primary adenocarcinoma of the tube, the greater part of the mucosa of the entire length and circumference of both tubes was involved; and, for the most part, the microscopic pattern was of the papillary type, but areas of the more solid papillary-alveolar development were found. In the instance of the carcinoma in situ of the Fallopian tube, grossly the Fallopian tube and ovary were very densely adherent and there was histological evidence of chronic inflammation. Microscopically, the process involved the epithelium of 2 of the glandlike rugae and parts of several others. The epithelium was truly stratified and there were marked elongation and hyperchromasia of the nuclei. Mitotic figures were frequent. Both the ciliated and the secretory cells were involved, but there was no invasion of the underlying blood vessels, lymphatics, or musculature.

#### Management and results

In 9 patients the initial operative procedure consisted of bilateral salpingo-oophorectomy with hysterectomy. In 3 instances (prior to 1940) the cervix was not removed. In the other 3 the initial operation consisted once of a unilateral salpingo-oophorectomy, once of a salpingectomy, and once of a bilateral salpingo-oophorectomy. At a later date more extensive operations were done in 2 cases, and metastatic lesions were found in both. Preoperative x-ray therapy had been given to one of the pa-

tients. Postoperative radiation therapy was administered in 10 cases, but its use was considered of equivocal value.

As one would anticipate with a malignant process which so completely evades diagnosis, the 5 year survival results are disappointing. Excluding the case of carcinoma in situ, 8 patients died of carcinomatosis within one to 4 years, but 3 patients survived 5 or more years, making a 5 year survival rate of 27 per cent. Except for the total hysterectomy and bilateral salpingo-oophorectomy with wide excision of the adnexa, the addition of more radical operation, especially pelvic lymphadenectomy, was considered of dubious value and probably not indicated because of the fact that, at the time of operation, in 2 cases, the metastatic lesions, small seedling type, were distributed over the peritoneal surfaces, especially of the intestine tract, and in 5 other cases the post-mortem examination revealed a similar but more extensive type of distribution of the metastatic lesions and no involvement of the pelvic lymph nodes.

#### Comment

The problem of treatment resolves itself into the same category as other genital tract malignancies at the present time. Earlier diagnosis offers the only satisfactory means of improving survival rates. The most constant diagnostic sign in all of the cases was the finding of a pelvic or adnexal tumor. The accepted principle that an adnexal mass in a woman more than 35 years of age requires operative investigation applies equally well in this situation. The use of hysterosalpingogram offers little, especially in the presence of chronic salpingitis.

Cytological screening studies of the cervical or endocervical fluids almost never give specific information. In 3 cases reported by Brewer and Guderian<sup>17</sup> and in 3 additional cases reported by Fidler and Lock,<sup>18</sup> the preoperative vaginal cytological study was positive and was the main contributing factor in the diagnosis of the tubal malignancy. In 5 of our cases one or more preoperative vaginal cytological studies were reported as

Class I or Class II. In the presence of no cervical or uterine pathology to explain a Class A-3 to 5 cytological report, a malignant process of the tube or ovary must be strongly suspected. A thorough investigation should include such preliminary procedures as bimanual examination under anesthesia, culdoscopy, or cul-de-sac visualization, but in most instances a laparotomy is necessary for diagnosis as well as for treatment.

At the time of operation, the lesions in our cases were rarely recognized because of the gross findings of hematosalpinx, pyosalpinx, or hydrosalpinx with multiple dense adhesions. This adds weight to the argument that the presence of a pelvic or adnexal mass in patients of this age group requires a total hysterectomy with bilateral salpingo-oophorectomy. We also fully agree with Peham,<sup>16</sup> and Hu, Taymor, and Hertig,<sup>11</sup> who have emphasized the fact that, because of the establishment of the modern,

more expectant treatment of chronic pelvic disease, an increasing number of carcinomas of the Fallopian tube will go undiagnosed until they reach the incurable stage.

### Conclusions

Twelve cases of primary carcinoma of the Fallopian tube, an incidence of 1.1 per cent among 1,087 genital tract malignancies, are reported. The corrected 5 year survival rate is 27 per cent.

The diagnosis was never made before operation. The most constant finding on examination was a pelvic or adnexal mass. In 6 of the 12 patients the initial complaint was vaginal bleeding.

The treatment of choice is total hysterectomy with wide excision of the adnexa. Postoperative irradiation is recommended although in this series its value could not be demonstrated.

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### Discussion

ABRAHAM F. LASH, Chicago, Illinois. Routine pelvic examination after hysterectomy when adnexa remain may determine the presence of a pelvic mass which is entirely as asymptomatic as an ovarian neoplasm in the early stage of development. This occurred in one in the authors' series of 12 and in 2 in our series of 10 at Michael Reese Hospital.

Positive Papanicolaou vaginal smears, when

the uterus is present, are significant in the absence of vaginal or uterine pathology. Corscaden, Brewer, and Falls have reported such an experience.

Culdoscopy, posterior colpotomy, and hysterosalpingography have been mentioned as diagnostic measures. No diagnosis has been reported in the literature based on such findings.

At laparotomy, particularly when hydrosal-

pinx, hematosalpinx, or nodulations of the tube are present, a frozen section is indicated to prevent incomplete operation. In one instance reported, the carcinoma of the tube was found in the segment of tube removed for sterilization. It is at times difficult to differentiate a tuberculous salpingitis from a carcinoma without the microscope. By establishing the diagnosis at operation, a second operation or inadequate surgical removal may be avoided.

In regard to therapy, it is the consensus that operation is the procedure of choice since the character of the condition makes it radioreistant. In the Lying-in series and in our series, preoperative x-ray therapy was utilized to no advantage. The poor results with operation are probably due to the extension of the lesion be-

fore diagnosis. The surgical effort should follow the principles of all cancer operations, which are wide dissection and removal of lymph nodes. Also, nitrogen mustard may be used intraperitoneally. Since preoperative and postoperative irradiation has not demonstrated its value, why use it?

DR. HAYDEN (Closing). The problem of the initial operation is not a very difficult one. The problem is really to prevent or control the spread. This spread is very characteristic and is to the peritoneal surfaces of the small and large bowel and liver. Possibly, postoperative intraperitoneal nitrogen mustard offers some hope. Certainly radiation has nothing to offer.



# Fibroma of the Fallopian tube

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TUMORS of the nonepithelial elements of the Fallopian tube, benign and malignant, are exceedingly rare. So infrequently are these lesions encountered that seldom is the diagnosis of a tubal neoplasm entertained prior to surgical exploration. The following case report is that of a fibroma of the Fallopian tube. In a review of the literature of the past 10 years, we have been unable to find any description of this entity.

## Case report

W. H., a 30-year-old single, white woman, was admitted to Bethany Hospital on March 17, 1958, complaining of severe, progressive dysmenorrhea which no longer responded to analgesics and hormone therapy. Her symptoms were of such magnitude that she had to be absent from work for about 4 days a month. Placebos gave no relief during the time when medication was effective. Menses began at age 13 and occurred regularly every 28 to 30 days; there was a moderate flow lasting 5 days. The onset of pain was always on the first day of her menstrual period. Pelvic examinations showed the uterus to be normal in size, shape, consistency, and position. The left adnexa were normal but on the right side a small tender mass was palpable. This mass was thought to be an ovarian neoplasm. There were no other noteworthy physical findings. On the tentative diagnosis of endometriosis in the pelvis and a chocolate cyst of the right ovary, laparotomy was performed. Under general anesthesia, a midline incision was made and carried down through the peritoneum. The uterus and both ovaries were found to be normal. On the right tube,

near the fimbriated end, attached only to the tube by a small pedicle and otherwise lying free, was a plum-sized gray solid tumor mass. The pedicle was clamped, cut, and ligated and the tumor removed. Presacral neurectomy was done in the classical fashion just below the promontory of the sacrum and the appendix was also removed in the routine manner. The patient made an uneventful recovery and was discharged on the eighth postoperative day. At the time of this report she had had 6 normal menstrual periods all entirely free of pain or discomfort.

**Pathological examination.** The surgical specimen consisted of an oval tumor mass (Fig. 1) which was 3.5 by 2.5 cm. and very firm in consistency. The outer surface of the tumor was bosselated with some fairly deep sulci. The tumor was pale pinkish gray to pale yellow gray in color. The surface made by cutting was pale yellow gray and there was a branching fibrous central stalk giving the appearance of a bisected cauliflower head. Some narrow slitlike spaces or



Fig. 1. Photograph of tumor which was attached to the fimbriated end of the Fallopian tube. On the left is the surface made by cutting and which shows a central branching stalk; on the right is the knobby capsular surface.

*From the Departments of Obstetrics and Pathology, Bethany Hospital.*

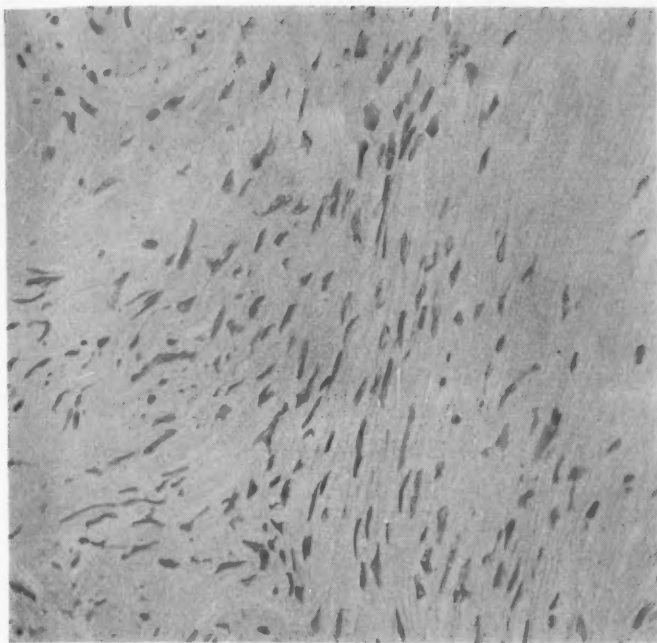


Fig. 2. Photomicrograph showing interlacing bundles of fibrous connective tissue and areas of hyaline degeneration. (Hematoxylin and eosin;  $\times 250$ .)

clefts were noted partially surrounding small nodules of tissue. Sections stained with hematoxylin and eosin showed the tumor to be covered by a fibrous capsule which appeared to be continuous with the underlying tissue. The tumor was composed entirely of interlacing bundles of dense fibrous connective tissue, which in some areas showed a marked degree of hyalinization (Fig. 2).

There was a lobulated pattern to the lesion under the scanning power, and higher magnification showed the clefts or slitlike spaces to be lined by a flattened cuboidal to low columnar epithelium. Sections stained with Masson trichrome stain showed the tumor to be composed entirely of fibrous connective tissue. The nuclei varied from spindle shaped to oval and no muscle elements were seen. Scattered small blood vessels were noted throughout the tumor.

#### Comment

Primary carcinoma, chorionepithelioma, and adenomyoma comprise the majority of the reported neoplasms of the Fallopian tube.<sup>1</sup> Strange as it may seem, leiomyomas occur but rarely even where the uterus is involved. In a series of 934 uterine tumors only one tubal myoma was found.<sup>2</sup> Of the anatomical regions of the Fallopian tube, the fimbriated extremity or infundibulum is the site least often involved.

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# Surgical treatment of complications resulting from irradiation therapy of cervical cancer

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THE management of problems created by the treatment of cancer of the cervix is often as challenging as, and more difficult to solve than, those of the original disease. In an occasional patient, the most difficult problems are only starting with cure of the disease by irradiation therapy. This paper is a report of our method for treating genital fistulas, proctitis, necrosis of the vagina and cervix, and skin degeneration caused by irradiation treatment.

Hoffman, Lewis, and Chamberlain studied 258 patients with carcinoma of the cervix treated with radium and x-ray from 1940 to 1946 and found that 35.5 per cent developed serious or moderate complications. They deduced that the main cause of the complications was too rigid standardization of irradiation therapy and questionable placement of radium.<sup>1</sup> Lewis and Chamberlain state that the improved recovery rate of carcinoma of the cervix from 28 to 46 per cent has apparently been attained at the cost of severe postirradiation complications in 14 per cent of survivors. The complications included fistulas, ureteral occlusions, intestinal injuries requiring resection or diversion operations, and massive tissue necrosis, often followed by complete vaginal closure. Their study suggested that the incidence of complications doubled when the radium dose exceeded 5,000 mg. hours.<sup>2</sup>

*From the Department of Obstetrics and Gynecology, University of Colorado Medical Center.*

## Irradiation proctitis

The first published report of rectal symptoms following irradiation therapy appeared in 1915.<sup>3</sup> In 1930, Buie and Malmgren introduced the term "factitial proctitis."<sup>4</sup> Kaplan reported on 62 patients with irradiation proctitis, which occurred in a group of 159 patients receiving irradiation for gynecologic pelvic malignancies.<sup>5</sup> More than 30 per cent of his patients had no symptoms despite the presence of mucosal changes. Rectal symptoms may occur as late as 7 years after treatment. Untreated rectal lesions usually heal in 12 to 24 months. Irradiation proctitis may be attributed to congestion and obliteration of blood vessels, caused by cessation of cell division with subsequent disintegration and absorption of cells followed by fibrosis or connective tissue replacement.<sup>6</sup> White and Finn found in their series that one out of every 6 patients had postirradiation proctitis with stricture formation.<sup>7</sup>

When both the external and the intracavitary irradiation are carefully conducted, irradiation proctitis may be minimized as a complication. Some degree of rectal irritation cannot be avoided and will be accompanied by varying degrees of lower bowel irritation. Diarrhea, rectal tenesmus, and bloody stools are signs of severe rectal injury from irradiation.

Rectal reactions often result from the faulty placement of the radium. Uterine retroversion may place the intrauterine applicator posteriorly and provoke this compli-

cation. The more usual causes are insufficient distance between the vaginal radium and the rectovaginal septum, slipped applicators, or insufficient screening. We use vaginal gauze packing soaked in barium solution to protect the rectovaginal septum and the base of the bladder. This is placed in such a manner as to displace the bladder anteriorly while displacing the rectum posteriorly from the radium applicators.

The rectal symptoms caused by the irradiation are related to the degree and progress of the rectal lesion. The pathologic lesion can be divided into three stages:

**Stage 1.** This stage is confined to edema and vascular congestion of the rectal mucous membrane, usually of the anterior wall, at the level of the cervix. This appears, under direct inspection, as a circumscribed area of thickening that is reddened and edematous and covered by a mucoid exudate. These signs are often accompanied by rectal bleeding, diarrhea, tenesmus, sphincter irritability, and a mucoid discharge.

**Stage 2.** This is the ulcerative stage, which results from thrombosis of small mucosal vessels. The mucosa becomes more thickened and is covered by exudate, and ischemia is more marked. Rectal pain is more severe and is associated with marked bleeding accompanied by diarrhea.

**Stage 3.** If the thrombosis and ulceration progress, then further necrosis, endarteritis, and secondary infection eventually lead to fistula formation or rectal stricture. Erosion into a large vessel may produce massive hemorrhage. Stricture formation leads to frequent and urgent desire for stool, incomplete evacuation, fecal or purulent discharge, and loss of blood.

#### Treatment

**Stage 1.** The symptoms in this stage usually respond to a bland, low-residue diet and mild analgesics. Belladonna and opium rectal suppositories will usually relieve the tenesmus and pain.

**Stage 2.** Patients of this stage are best treated in the hospital, with strict bed rest,

heavy sedation, soft bland diet, warm rectal irrigations with  $\text{KMnO}_4$  or saline, and mineral oil orally. Also of value are hot boric acid compresses to the perineum, rectal instillations of warm olive oil, and cortisone rectal suppositories.<sup>8</sup>

**Stage 3.** If the above regimen does not control the symptoms, then the fecal stream should be diverted by a temporary colostomy. It is extremely important that the transverse colon be used instead of the sigmoid colon. If a rectal pull-through procedure is elected at a later date, the resultant scarring and shortening of the mesentery may make the sigmoid colon too short for a pull-through operation and a permanent colostomy will be necessary. If the transverse colon is used, a long mobile segment of terminal colon remains for a later pull-through procedure.

The following 4 patients' clinical histories and their surgical treatment are given to illustrate the principle of rehabilitation surgery that may be necessary after irradiation injuries sustained by the rectum during the course of treatment for cancer of the cervix. Each of these 4 patients was cured of the cancer, but the irradiation complications posed problems of major degree for solution.

**Case 1.** This patient (C.G.H. No. 78845) was a 51-year-old woman who developed carcinoma of the cervical stump, Stage I,\* 6 years after a supracervical hysterectomy and was treated with cobalt needles. Intractable rectal pain, bleeding, and tenesmus followed and it became necessary to perform a transverse colostomy 4 months after treatment was completed, because of severe irradiation proctitis. Diarrhea and pain associated with the colostomy and a partial small bowel obstruction continued. Sigmoidoscopy later showed an area of stenosis of the rectum, which was friable and which bled easily. Seven months after the colostomy, a pull-through of the distal sigmoid loop was performed and the distal segment of injured rectum was resected to within 4 cm. of the anal sphincter (Figs. 1 and 2). The technique of this operation is de-

\*All stages mentioned throughout are according to the International Classification.



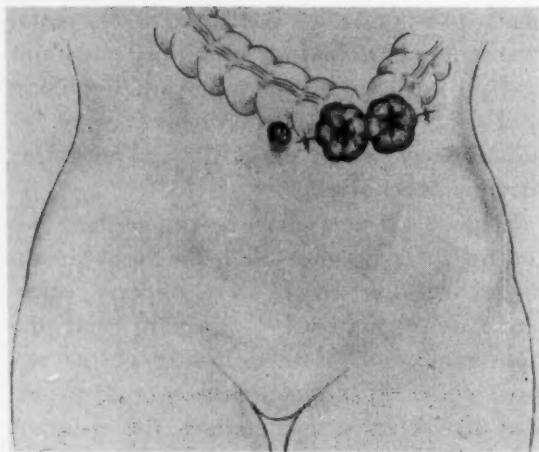


Fig. 1. Double-barrelled colostomy—the type of temporary colostomy we prefer in diversion of the fecal stream.

scribed in detail by Babcock and Bacon.<sup>9</sup> The rectal sphincter and 3 to 4 cm. of distal rectum must be available in order for a pull-through procedure to function properly.

This patient had chronic bladder complaints that were also secondary to the cobalt needle exposure. This was treated by bladder sedatives, with only partial success. This patient now has essentially normal bowel function, except for increased constipation, as compared to the period before the cancer of the cervix was treated.

**Case 2.** This patient (C.G.H. No. 56939) was a 37-year-old white woman with epidermoid carcinoma of the cervix, Stage II, treated by irradiation. Eight months after treatment, the patient experienced rectal bleeding, pain, and tenesmus, and a diagnosis of irradiation proctitis was made. This was treated with bland diet, mineral oil by mouth, mild analgesics, and rectal suppositories, which gave temporary relief. The patient re-entered the hospital with severe rectal tenesmus, bleeding, elevated temperature, and generalized cellulitis. Conservative measures failed to relieve the rectal symptoms, and a transverse colostomy was performed. Diversion of the fecal stream was accompanied by progressive healing of the rectal lesion. Six months later the distal segment was tested by having the patient insert Cream of Wheat into the stoma. Following this, however, the pain, bleeding, and tenesmus recurred. It will now be necessary to resect the sigmoid colon and perform a pull-through procedure.

**Case 3.** This patient (C.G.H. No. 3331) was treated with radium and x-ray for a Stage II epidermoid cancer of the cervix in October, 1947. In March, 1948, she developed rectal tenesmus, hemorrhagic proctitis, and rectal frequency. This was treated with belladonna and opium rectal suppositories, mineral oil by mouth, and a bland diet. By May, 1948, a stricture formation was apparent in the region of the rectum, and diarrhea was present. Rectal biopsy at that time revealed irradiation proctitis with ulceration, which soon developed into a recto-vaginal fistula. A temporary transverse colostomy was performed, after which the rectal ulcer completely healed. A pull-through of the sigmoid was done with resection of the stricture and fistula in April, 1948. Four months later the temporary colostomy was closed and the patient since has had normal bowel function.

**Case 4.** This patient (C.G.H. No. 67828) was a 42-year-old Spanish-American woman who was diagnosed as having epidermoid carcinoma of the cervix, Stage II, in September, 1954, and treated with irradiation. Six months after treatment she began to have severe rectal pain, tenesmus, and bleeding, which gradually progressed, and in June, 1956, she was found to have severe vaginal stenosis, rectal stricture, and irradiation proctitis. This gradually progressed and she then developed a large rectovaginal fistula, which became secondarily infected and which was associated with bouts of cystitis and pyelonephritis. A transverse colostomy was performed to divert

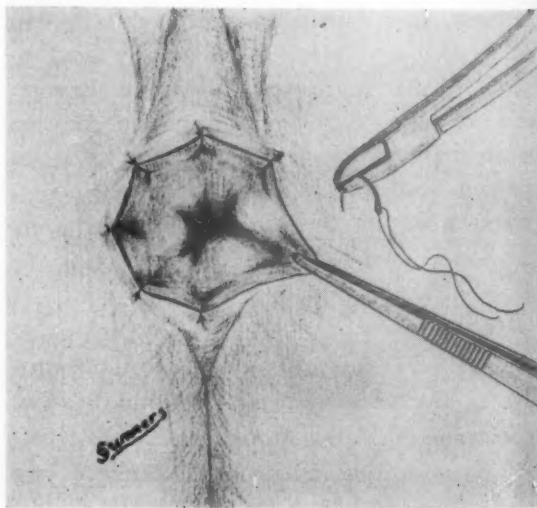
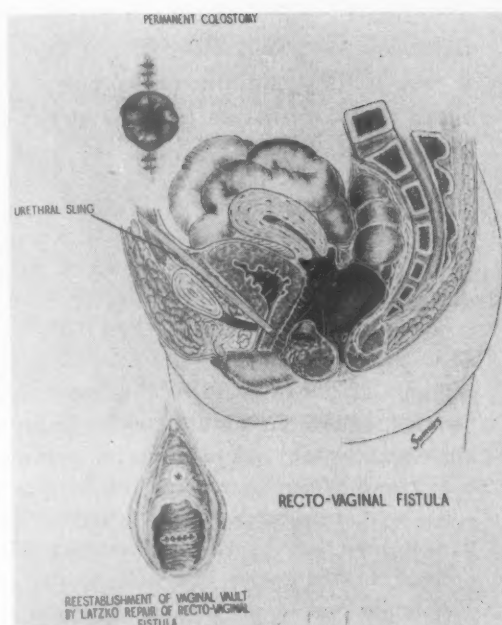


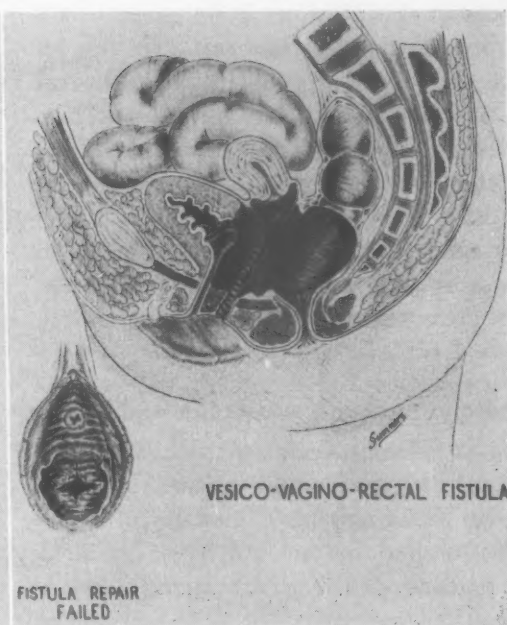
Fig. 2. The final stages of the pull-through procedure.



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**Fig. 3.** Central figure illustrates the original recto-vaginal fistula. The top insert shows the permanent colostomy, the distal segment having been resected when the pull-through procedure was abandoned. The lower insert shows the recto-vaginal fistula closed by the Latzko technique.

the fecal stream in preparation for possible closure of the large rectovaginal fistula. Six months later it was found that despite all attempts to sterilize the local area, it was continually infected and the repeated attacks of cystitis and pyelitis further compounded the problem. A fistulous tract between the distal and proximal colostomy loops beneath the skin was found, and continual contamination of the perineal area was taking place. This small opening was closed and the infection surrounding the invaded area subsided. Six months later the rectovaginal fistula was closed by the Latzko technique (Fig. 3). A pull-through operation was entertained at this time, but it was discovered that the patient had no anal sphincter, it having previously been destroyed by child-birth lacerations. Therefore, it was decided that she would be better off with a permanent colostomy. Another complaint was almost continual urinary incontinence, secondary to the scarring and contracture of the bladder neck. The patient was placed on antibiotics in an effort to sterilize the urinary tract, and then a Goebell-Stoeckel urethral sling operation, with use of ox



4

**Fig. 4.** Center insert shows the original vesico-vagino-rectal fistula. The lower insert illustrates the failed repair of this large fistula.

fascia, was performed. The distal colostomy loop was resected. At the present time, the large infected perineal area is clean. There is no drainage through the vagina and there is a normal functioning abdominal transverse colostomy.

**Principles of surgical treatment.** The most severe problems often must be treated by complete rest of the rectum. This is gained through performance of a transverse colostomy. This should be done near the hepatic flexure, so as to provide a long, mobile segment of colon should a rectal resection and pull-through colon-to-rectal-sphincter anastomosis be necessary. Six months should elapse before the temporary colostomy is closed. It takes this long before maximum healing of the rectal area is completed. If the patient continues to have rectal tenesmus, pain and bleeding on testing the distal colostomy loop, if severe rectal stricture results, or if a rectovaginal fistula develops, then resection of the rectosigmoid and a pull-through procedure are indicated. The

pull-through procedure is accomplished by resection of the affected rectosigmoid colon with preservation of the distal 4 cm. of rectum and anal sphincter. The normal colon is then pulled through the rectum and the anastomosis is performed from below, under no tension, with interrupted sutures. Extreme care must be used in taking biopsy specimens in these cases, for bowel perforation and massive bleeding have occurred from seemingly insignificant biopsy sites.

#### **Irradiation necrosis of vagina and cervix**

The pathologic process of irradiation necrosis of the cervix and upper vagina is persistent tissue necrosis secondary to vascular destruction. There are two types of ulcers which occur in postirradiated patients—superficial and deep. The superficial ulcer occurs after healing of the irradiated tissue has taken place. Primary healing occurs in this avascular area, but the progressive ischemia finally leads to ulceration of the cervix or vaginal mucosa.

The deep ulcer is characterized by a large, ragged, craterlike area surrounded by dense induration and secondary inflammation, the center of which continues to slough and bleed. It is difficult to differentiate this type of lesion from recurrent carcinoma or malignancy which fails to respond to irradiation. Exfoliative cytology is of little value because of tissue necrosis and infection. Pelvic examination under anesthesia and extensive biopsy procedures are most helpful in differential diagnosis. Local débridement and antibiotic treatment are helpful in some patients. Usually healing will not occur, even after several months of local treatment, but conservative treatment should be followed for 3 to 4 months. If healing does not occur, and pain and vaginal discharge continue, the area of ulceration must be excised.

We have used both the vaginal and the abdominal approach for excision of irradiation ulcers. The vaginal approach has the advantage of allowing direct vision of the area to be excised. It may be necessary to

provide a split-thickness skin graft to leave a vagina of sufficient length after wide excision of the vaginal fornices. Case reports 5 and 6 illustrate the management of patients with irradiation necrosis of the cervix and vagina.

**Case 5.** This patient (C.G.H. No. 102521) was a 34-year-old white woman who was diagnosed as having Stage I carcinoma of the cervix in October, 1956, and was treated with deep x-ray and radium. In January, 1957, she noticed postcoital bleeding and heavy vaginal discharge. Examination showed a large area of necrotic tissue replacing the cervix. Biopsy specimens taken under anesthesia were negative and a diagnosis of irradiation necrosis of the vagina and cervix was made. In February, 1958, the patient underwent a vaginal hysterectomy with excision of the upper one half of the vagina. The upper end of the vagina was covered with a split-thickness skin graft taken from the thigh. Local and systemic antibiotics were used postoperatively and two thirds of the skin graft survived. The patient re-entered the hospital in March, 1958, complaining of perirectal and deep pelvic pain. Pelvic examination revealed a necrotic area at the vaginal apex, with tenderness of the parametria with some firmness and induration of the adnexal regions. This was treated with penicillin and streptomycin. She was discharged 10 days later. The patient was given oral estrogen therapy. She now has a satisfactory functional vagina of normal depth.

**Case 6.** This patient (C.G.H. No. 103237) is a 35-year-old white woman who had a previous supracervical hysterectomy. Stage I carcinoma of the cervix was diagnosed and treated by irradiation in June, 1957. At the end of therapy she had brawny induration of the skin over the abdominal area and diarrhea secondary to irradiation therapy. The patient was admitted to Colorado General Hospital in March, 1958, because of acute lower abdominal pain with vaginal bleeding of 7 days' duration. Physical examination at that time showed pulse 140, temperature 38.8° C., and marked tenderness in both lower quadrants of the abdomen. Pelvic examination showed induration and necrosis of the posterior vaginal wall. Vaginal and cervical biopsy specimens were taken. These showed the lesion to be irradiation necrosis. In April, 1958, the ulcerated area replacing the cervix was excised with a wide cuff of vagina. The post-



operative course was complicated by a marked febrile course which required a prolonged stay in the hospital. The pelvic cellulitis gradually cleared and the vaginal apex healed by primary intention. The patient is now taking oral estrogens and has a functional vagina.

**Principles of treatment of irradiation vaginal ulcer.** The vaginal and cervical ulceration should be carefully treated with débridement, proper antibiotic therapy, pelvic heat, and oral estrogens. Healing will occasionally occur. If the patient continues to have pain and discharge and the local area does not show signs of progressive healing, then wide vaginal excision of the ulcer to an area of better blood supply is necessary. An Ollier Thiersch split-thickness graft with several small perforations for drainage, packed in place with gauze soaked in antibiotic ointment to act as a splint, works well for patients where the vaginal length must be preserved. After healing has occurred, intercourse should be resumed so as to prevent stricture and atrophy of the vagina.

#### Vesicovaginal-rectal fistulas

The problems of surgical technique, physiology, bacteriology, and electrolyte balance which must be faced in correcting a combined vesicovaginal-rectal fistula are legion.

The surgical problem is compounded because of poor blood supply, inelasticity of the tissue, the close proximity of the ureteral orifices, the possibility of persistent carcinoma, and the fact that healing of heavily irradiated tissue is uncertain. Too often the examining physician makes a diagnosis of hopeless pelvic cancer in a patient who may be free of cancer but who is suffering from one or more genital fistulas. The patient who looks well and who maintains body weight but continues to have pain usually has irradiation reaction and not recurrent or persistent cancer.

Brack and associates<sup>10</sup> summarized their experiences in 402 cases of carcinoma of the cervix treated from 1943 to 1948 and found 57 fistulas (7.05 per cent); vesicovaginal 5.4

per cent, rectovesicovaginal 2 per cent, ureterovaginal 0.5 per cent, and rectovaginal 6.2 per cent. Fistulas that develop in Stage I and II lesions must be attributed to poor irradiation technique. They found 15 per cent severe ureteral obstruction and 20 per cent bladder lesions of serious clinical significance. They concluded that the presence of lesions of the upper urinary tract before treatment in patients with carcinoma of the cervix is of grave prognostic significance. In 402 patients studied, of those with normal pyelograms 49.5 per cent were alive in 5 years. If hydronephrosis was present, then 25.5 per cent were alive in 5 years.

The following 3 patients' clinical histories (Cases 7, 8, and 9) illustrate the problems of vesicovaginal-rectal fistulas, which are complications of irradiation therapy. The surgical management is outlined.

**Case 7.** This patient (C.G.H. No. 102694) was a 50-year-old white woman who first had vague symptoms in January, 1955, and vaginal bleeding in September, 1955. A diagnosis of Stage III carcinoma of the cervix was made and therapy was completed in March, 1956. The amount of irradiation given to this patient (10,000 mg. hours) was, in our opinion, excessive. A rectal fistula developed several months later and it was thought that the disease had recurred. A sigmoid colostomy was performed in January, 1957, and the patient was transferred to a terminal cancer home. A vesicovaginal fistula developed shortly thereafter. The patient suffered from unremitting pelvic pain and required constant narcotics for partial comfort. The patient was admitted to Colorado General Hospital in March, 1958, because of severe pelvic pain, marked weight loss, and a profuse and foul-smelling vaginal discharge. The vesical and rectovaginal fistulas were present with the accompanying incontinence. There was no evidence of recurrent cancer to be found by physical examination, biopsy, or x-ray examination. Repair of the fistulas was attempted in March, 1958. The repair of the rectovaginal and vesicovaginal fistulas did not succeed. An ileal bladder was constructed and the distal colostomy loop was resected (Fig. 4).

The patient was then cured of the narcotic addiction. She has gained 20 pounds and has



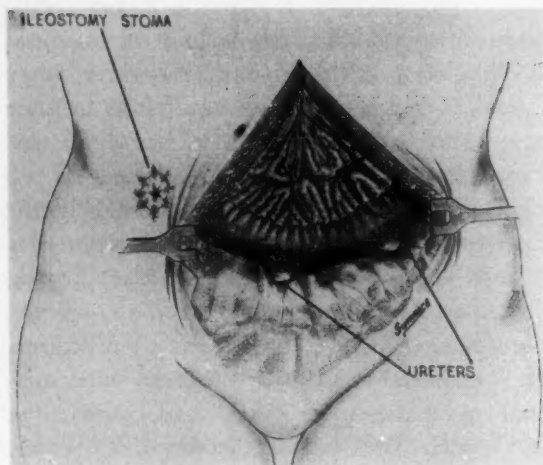


Fig. 5. The completed ileal bladder. A segment of distal ileum 12 to 14 cm. in length is isolated and the proximal end closed. The ureters are then severed 4 cm. below the pelvic brim and anastomosed to the ileal loop. The distal end is then brought through the skin and a Bongort bag attached around the stoma.

a well-functioning ileal bladder as well as the previously well-functioning colostomy (Figs. 4 and 5).

**Case 8.** This patient (C.G.H. No. 86586) was a 38-year-old white woman. In December, 1947, she was treated with x-ray and radium in another institution for squamous cell cancer of the cervix, Stage I. By February, 1949, she had developed a vesicovaginal and a rectovaginal fistula. Her physician considered that she was dying of persistent pelvic cancer. This conclusion was based on clinical findings, not biopsy evidence. The pelvic examination revealed clinical findings compatible with Stage IV cancer of the cervix. We first saw the patient in September, 1956, and were amazed that she was still alive after 7 years of presumed terminal disease. During this time she had become addicted to morphine and was thoroughly miserable from the fistulas and the accompanying pelvic infection. Multiple biopsies of the pelvic area and the fistulous tracts showed only inflammatory reaction. The first step in her surgical rehabilitation was to perform a transverse colostomy in order to divert the fecal stream from the vagina and rectal area. This was done in September, 1956. In January, 1957, the vesicovaginal fistula was closed and a "pull-through" operation was performed at the same time. Scarring of the rectum made primary

closure of the large rectovaginal fistula impossible. The area of stenosis was resected and the distal segment of the sigmoid was circularly attached to the rectal mucosa, 2 cm. above the anal sphincter. The patient was discharged from the hospital in March, 1957. The morphine addiction was then successfully treated. She was relieved of all pelvic pain and became free of the fistula problem for the first time in over 7 years. In June, 1957, the patient re-entered the hospital for surgical closure of the temporary colostomy. She is now free of disease, has gained 55 pounds, and is leading a normal life in all respects (Fig. 6).

#### Principles for treating genital fistula.

These patients must be thoroughly studied in order to ascertain the presence or absence or residual or recurrent cancer. This can usually be accomplished through x-ray survey of the skeleton and multiple biopsies of the pelvic area. If a rectovaginal fistula is present, a temporary transverse colostomy must be performed so that the fistulous area can be made as free from infection as possible. The rectovaginal fistula may have

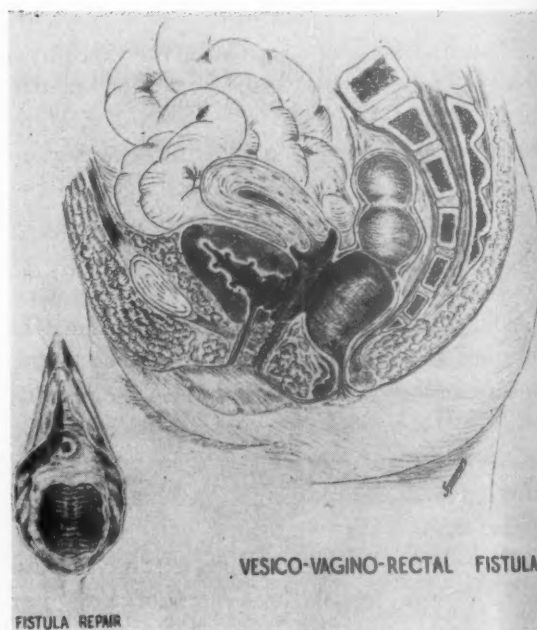


Fig. 6. The original vesicovaginal-rectal fistula. The lower insert illustrates the successful repair of the vesicovaginal fistula. A pull-through procedure with closure of the rectovaginal fistula was performed at a second operation.

to be treated by segmental resection of the involved rectum followed by sigmoid-to-rectum anastomosis. The vesicovaginal fistula is treated by wide excision of the fistulous tract and approximation of tissue without tension. It is often necessary to reimplant a ureter into the dome of the bladder so as to avoid ligation with repair of the fistula.

### **Irradiation necrosis of the skin**

Skin reaction depends upon the dose, protraction, and quality of external irradiation. When an average skin dose is given, it will usually be followed by a dry, bronzing reaction, which in the majority of patients will progress to a moist desquamating reaction, which heals readily in one to two weeks. When the irradiation dose is excessive or when the patient happens to be hypersensitive to irradiation, a large area of necrosis results. This may occur within a few weeks or even years after completion of the x-ray therapy.

The following patient's history and the management of the complications illustrates this type problem.

**Case 9.** This patient (C.G.H. No. 38973) was a 46-year-old white woman who was treated for Stage I carcinoma of the cervix in November, 1950, with radium and x-ray. Eight months following treatment she noticed that the skin over the lower abdomen was red and very tender. About this time the center of this red, painful area became ulcerated and a small abscess subjacent to this area broke through and drained over the abdominal wall, thus compounding the problem. The local area was treated with antibiotics and débridement and when the secondary infection subsided an ulcerated area approximately 6 cm. in diameter remained. It was decided that a full-thickness pedicle graft would be needed to cover this large area and subsequently on either side of the ulcerated area two pedicle flaps were made. One month after these skin pedicles were made the grafts were transferred over the ulcerated portion and sutured together. The area then healed by primary intention and the patient left the hospital with a well-healed abdominal wall.

**Principles of surgical treatment of skin necrosis.** If pain and necrosis continue, wide block excision of the involved skin area is necessary. The skin lesion usually extends through the subcutaneous fat to the fascia. A pedicle graft is most frequently the best method for treating the area, but only after complete excision of the necrotic skin and subcutaneous tissue.

### **Conclusions**

1. A patient who has irradiation necrosis following treatment for cancer should not be discarded as hopeless or diagnosed as having recurrent carcinoma without definite biopsy evidence.
2. The fact that patients continue to have pain, but thrive and gain weight in spite of it, is fairly good clinical evidence that their problem is one of irradiation necrosis and not recurrent disease.
3. A necrotic lesion of the vagina, even including the fistulous tracts, should not be assumed to be cancer without biopsy evidence.
4. In order to effect a surgical cure in patients with irradiation proctitis or multiple fistulas, the fecal stream must be diverted for 6 months as a preliminary step in preparing the local area.

### **Summary**

The surgical principles involved in the diagnosis and correction of necrotic lesions following irradiation therapy have been discussed. These include skin necrosis, irradiation proctitis, irradiation necrosis of the cervix and vagina, and multiple genital fistulas. Illustrative cases of each category have been presented and the method of treatment used covered in detail.

We wish to express our thanks to Kelvin Kessler and Thomas Sumners, senior medical students, for their technical assistance and aid in preparing the illustrations.

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# Extensive myomectomy

Review of 157 cases

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EXTENSIVE myomectomy deserves a more important place in the armamentarium of the gynecologist and the general surgeon. This operation is being done sporadically by some general surgeons and more often by gynecologists. However, judging from the dearth of literature on the subject, as well as the paucity of papers being presented, too little attention is being given to this humane, reparative type of surgery.

By extensive myomectomy we refer to that operation where extensive or complete invasion of the myometrium is required for the removal of one or several fibroids of appreciable size. Cases of superficial subserous tumors or where the fibroid is pedunculated into the peritoneal cavity or cervical canal are not considered in our discussion or included in the series to be presented.

The first recorded myomectomy was done vaginally by Ammusset, in France, in 1840. Similar attempts by others were accompanied by poor results, and the procedure fell into disuse. About this time, it was noted that fibroids had more or less of a capsule and, if easily accessible and superficially situated, they could be removed safely. However, if they were multiple, deeply embedded, or located near blood vessels, their removal was hazardous. The operation, therefore, had a very restricted scope, with sepsis and hemorrhage frequent complications.

*From The New York Polyclinic Hospital.  
Presented before a meeting of the New  
York Obstetrical Society, Oct. 14, 1958.*

Alexander, of Liverpool,<sup>1-3</sup> during 1897 and 1898, tried to popularize extensive abdominal myomectomy. He presented 3 papers and emphasized that the underlying principle for success lay in the removal of all the deeper tumors through one incision. His mortality rate of 9 per cent compared favorably with that of hysterectomy at the time. His views were not accepted, however, and the operation, as well as interest in it, died.

At the beginning of the twentieth century, with improved asepsis and greater use of transfusions, the number of myomectomies increased. Howard A. Kelly<sup>4</sup> and C. P. Noble<sup>5</sup> became strong and active proponents of this procedure.

Vineberg,<sup>6</sup> Mayo,<sup>7</sup> Miller,<sup>8</sup> Bonney,<sup>9</sup> and others reported large series of extensive myomectomies with mortality rates comparable with those of hysterectomy.

Table I. Deaths following myomectomy

Author and year	Operations	Deaths
Vineberg <sup>6</sup> (1921)	120	0
Mayo <sup>7</sup> (1922)	909	3
Bonney <sup>9</sup> (1945)	806	9
Miller <sup>8</sup> (1932)	141	1
Counseller <sup>10</sup> (1937)	523	6
Rubin <sup>11</sup> (1942)	481	9
Finn and Muller <sup>12</sup> (1950)	432	0
Munnell and Martin <sup>13</sup> (1951)	370	1
Brown, Chamberlain, and Te Linde, <sup>14</sup> (1956)	335	1
Lardaro (1958)	157	1
Total	4,274	31*

\*Mortality rate: 1 in 137 or 0.7 per cent.

With these favorable reports and the growing tendency toward conservatism, ex-



tensive myomectomies gradually became more popular among gynecologists but never met with great favor among the general surgeons.

### Conservation of reproduction

Some authors stressed the value of myomectomy in the conservation and re-establishment of the reproductive functions. Vineberg<sup>6</sup> reported a 27 per cent conception rate in 120 cases. Miller<sup>8</sup> stated that 36 per cent of his 141 patients, all under the age of 38 years, subsequently bore children. The Bonn Clinic<sup>25</sup> reported only 11 women pregnant out of 78 on whom myomectomies were performed. As these myomectomies in many instances were done without prior evaluation of the husband's fertility, one assumes that a fair proportion of the failures were due to male infertility.

Throughout this period Bonney<sup>15-19</sup> was a persistent and successful proponent of extensive myomectomies. His exposition of an almost bloodless technique made this operation more feasible and desirable. He emphasized that surgery's ideal is cure without deformity or loss of function. Myomectomy falls into that category. In general, it is a more difficult and painstaking procedure than hysterectomy. It requires more thought, greater fortitude and technical skill, and, above all, patience. Some of its inherent dangers, such as sepsis and hemorrhage, have been decreased by antibiotics and the liberal use of blood transfusions, but the operation is time-consuming and unspectacular; it may be bloody, and it is always fraught with danger. It requires deep appreciation of the sanctity of tissues and meticulous attention to minutest details. These factors, plus the strong desirability to remove the cervix, a worthy and justifiable aim in hysterectomy, have militated against the greater employment of myomectomy.

Myomectomy, however, still deserves greater consideration and utilization than it has enjoyed. This is especially so in this age of reconstructive surgery. It has its limitations and contraindications, but there are

definite indications which should be carefully considered in every instance.

### Indications

Physicians have no right to decide arbitrarily when a woman should cease to bear children. The removal of the function of childbearing in the single girl or in the nulliparous up to the approximate age of 40, or in a woman who desires or may later desire to bear more children may inflict spiritual and emotional trauma on top of physical injury. The psychic and emotional effect on some of the husbands must also be considered. Extensive myomectomy is presented not as a substitute for hysterectomy but as an alternative in those instances where the patient's best interests are thus served. The patient's wishes, where reasonable, should be taken into consideration. The conservation of the menstrual function, especially in young or unmarried women, is a case in point. Normal ovarian function is better assured by myomectomy than by hysterectomy. The psychological and psychiatric impact of the premature surgical menopause on some women must be evaluated.

In myomectomies, certain precautions and preliminary investigations must always be employed. Any patient on whom myomectomy is contemplated should have a thorough survey of the entire genital tract, including cytologic studies and, where indicated, multiple biopsies of the cervix and endocervix. Infection of the cervix should be eradicated before operation.

Table II. Risk of sarcoma

Author	Myomectomies	Sarcomas	Outcome
Bonney <sup>9</sup>	806	1	Died
Rubin <sup>11</sup>	481	5	Survived
Finn and Muller <sup>12</sup>	432	1	Survived
Brown, Chamberlain, and Te Linde <sup>14</sup>	335	1	Not mentioned
Lardaro	157	0	—
Total	2,211	8*	

\*Incidence: 1 in 276 or 0.4 per cent.

A dilatation and curettage should precede all myomectomies. Whenever there is the slightest question of uterine malignancy, the curettage should be done early enough before laparotomy to insure proper evaluation of the curettings. Preoperative hysterosalpingography is being employed more frequently. The fractional technique with nonoily media is to be preferred.

The possibility of uterine sarcoma or sarcomatous degeneration, though remote, must be borne in mind.

### Contraindications

Extensive myomectomy is generally contraindicated in women over 45 years of age and in those at the approximate age of 40 who are not desirous of any or more children and are willing to have a total hysterectomy.

It should not be done in patients with extensive pelvic inflammatory disease or diffuse endometriosis where either conservation of ovarian function or of reproduction cannot be accomplished with safety to the patient and the alleviation of symptoms. Any suspicion of malignancy arising at the time of operation is, of course, a contraindication. Finally, there are patients with such extensive fibroids and such marked distortion of anatomy that safer conservative operation appears impossible. In such instances, it is better to retreat than regret, bearing in mind the over-all welfare of the patient. Adenomyoma of the uterus, if localized so as not to involve the entire uterus, does not contraindicate a reparative operation.

Bonney performed and advocated extensive myomectomies during cesarean sections. I have limited this procedure to 3 cases where fibroids protruded into the uterine incision and interfered with closure.

Rubin,<sup>11</sup> Berkeley and Bonney,<sup>20</sup> and others performed myomectomies on the pregnant uterus even before the period of viability of the fetus. Davids<sup>21</sup> states this was done 35 times at the Mt. Sinai Hospital between the sixth and eighteenth weeks of pregnancy and that 23 or 65.7 per cent

went to term. We have not found occasion to employ this procedure.

### Technical considerations

The following technical procedures will aid in the performance of extensive myomectomies.

1. Complete asepsis. This is of utmost importance, and its attainment is facilitated by clearing any endocervicitis before operation.

2. Obtain all possible hemostasis and control of oozing. In many cases, no special precautions will be necessary. Though in some instances the amount of oozing and bleeding is surprisingly moderate, in others it is copious, persistent, and excessive, requiring blood replacement.

Compression by ring forceps of both infundibulopelvic ligaments often helps. In others, compression of both uterine arteries just above the internal cervical os will be necessary. For this purpose, Bonney's clamp or Rubin's pericervical tourniquet technique<sup>22</sup> may be used, depending on circumstances. Bonney's clamp, however, is often difficult to apply, and some operators fear thrombosis, embolism, or trauma to broad ligament structures with either method.

In the last several years, attempts have been made to control bleeding chemically. With others we have used Pitocin infusions with some success but with inconclusive results. Douglas' group at Cornell University Medical College and the New York Hospital has been injecting vasopressin directly into the myometrium around the base of the myomas with satisfactory results. The recent preliminary report of Dillon and associates<sup>23</sup> from that institution on the hemostatic effect of vasopressin in gynecologic surgery suggests that blood loss in extensive myomectomies may be controlled chemically.

3. Find the proper line of cleavage in the enucleation of fibroids. Morcellate large fibroids during enucleation.

4. Seedlings or tiny myomas may be removed best by tunneling from one raw surface or enucleation cavity directly onto the

tumor which is then grasped and withdrawn by Allis clamps. Such tunnels usually contract, do not bleed, and rarely require suturing.

5. In all instances where there is any doubt concerning complete removal of all myomas, open the uterine cavity. This will assure the detection of any residual endometrial pathology not removed by curettage and will permit better palpation of the uterine wall for small fibroids or seedlings. Many small submucous or intramural fibroids will be found in this way. This procedure was almost routine in our series. Israel and Mutch<sup>24</sup> and other recent writers also recommend this.

6. Obtain a maximal amount of enucleation through a minimal number of incisions, preferably one.

7. Keep in mind the danger of thrombosis and embolism. This can be decreased by minimal crushing and trauma to tissues and by the elimination of unnecessary clamping, mass ligature, and dead spaces.

8. Secure complete obliteration of enucleation cavities with elimination of dead spaces. Partitions between enucleation cavities may be excised to facilitate better coaptation of cavity walls and leave a minimal amount of devitalized tissue.

9. When there are myomas in both uterine walls, first remove those on the anterior wall and then approach the posterior ones by the transcavitary route. If the myomas on the posterior wall are many or extensive, it may be desirable to form a posterior uterine flap, after the manner of Bonney's hood operation.

10. Try to avoid posterior wall incisions. Nearly all complications after myomectomy are the result of posterior wall incisions or of oozing into the enucleation or peritoneal cavity. These may cause shock out of proportion to the blood loss, as well as pyrexia, intestinal distention, and intestinal paralysis.

11. On reconstructing the uterus, try to leave it only a little larger than normal. This allows for normal postoperative involution. However, do not remove too much

uterine wall until sure of easy coaptation.

12. Try to prevent adhesions, especially to the small gut. This means meticulous peritonization. Aids to this are: (a) use of peritoneal bladder flap; (b) use of round ligaments; (c) placement of omentum over exposed traumatized areas; (d) employment of Bonney's hood operation.

Fear of complications has undoubtedly deterred operators from the liberal employment of extensive myomectomies. Our early experience is a case in point.

In 1935, we performed an extensive multiple myomectomy on a single girl about to be married, who had fibroids up to the level of the umbilicus. She never married as she developed a fatal pulmonary embolus. Reacting to this, we refused to perform the operation on 2 or 3 other patients. Later that year we performed a hysterectomy on a similar type of uterus, in a 28-year-old unmarried girl. Though she subsequently married and had a successful emotional and sexual life, she eventually was divorced, in part because of her inability to bear children. These 2 incidents are cited as extreme possibilities which may cause us to vacillate in deciding between myomectomy and hysterectomy. Since that time, we have performed 157 extensive myomectomies with no other deaths.

**Table III.** Number of patients operated upon (1935-1958)

1935-1942	21
1942-1947	24
1947-1952	37
1952-1954	28
1955-1958	47
Total	157

### Recurrence

The recurrence rate will depend chiefly on the thoroughness with which fibroids and fibroid seedlings, even down to those the size of BB shots, are removed.

Bonney's<sup>9</sup> experience led him to conclude that "seeds of fibroids are most commonly laid down between 28 and 33 and that after

Table IV. Recurrences and hysterectomy

Period of operations	Years of follow-up	Patients operated upon	Asymptomatic recurrence		Recurrence requiring hysterectomy		Total recurrences	
			No.	%	No.	%	No.	%
1957	1	10	0	0.0	0	0.0	0	0.0
1955-1956	2-3	37	1	2.7	0	0.0	1	2.7
1952-1954	4-6	28	1	3.6	0	0.0	1	3.6
1947-1952	6-10	37	4	11.0	2	5.4	6	16.0
1942-1947	11-15	24	0	0.0	4	16.7	4	16.7
1935-1942	16-23	21	4	19.0	4	19.0	8	38.0
Total		157	10	6.4	10	6.4	20	13.0

Table V. Recurrence after pregnancy

Period of operations	No. of patients	No. desiring children	No. becoming pregnant	Pregnancies	Abortions	Children born	Asymp-tomatic recur-rences	Hysterec-tomy after pregnancy
1935-1942	21	12	8	8	1	7	0	0
1942-1947	24	12	10	14	2	12	1	0
1947-1952	37	16	7	13	2	11	2	1
1952-1954	28	12	8	13	3	10	0	2
1955-1956	37	14	12	15	3	12	3	1
1935-1957 (Total)	147	66	45	63	11	52	6	4

33 the chances of new seedlings rapidly diminish until after 36 they are practically nonexistent." Bonney's recurrence rate was under 4 per cent, but he explains his very low incidence by his adherence to Alexander's dictum of "ransacking the uterus."

Fibroids without symptoms or requiring hysterectomy very often occur after the primary purpose of the myomectomy has been accomplished. Table V is illustrative.

Thus, of the 147 patients operated upon from 1935 to January, 1957, 66 were desirous of having children. Forty-five became pregnant 63 times and had 11 spontaneous abortions. Forty-two of the 45 patients delivered 52 living children. Six of the 66 subsequently developed asymptomatic fibroids and 4 others required hysterectomy. Only 10 of the 66 had children previously and 2 others had spontaneous abortions.

Table VI. Comparative results following myomectomy

Author	No. of cases	Subsequent pregnancy (%)	Relief of sterility (%)	Recurrence of fibroids (%)	Reoperation required (%)
Bonney <sup>9</sup>	806	38.0	38	Less than 4 per cent	1.8
Ahlthrop <sup>26</sup>	?	31.0	24	24.8	5.0
Counseller <sup>10</sup>	523	35.0	—	20.0	—
Miller <sup>8</sup>	141	36.0	—	—	3.0
Finn and Muller <sup>12</sup>	432	25.0	36	23.0	12.0
Munnell and Martin <sup>13</sup>	370	26.0	47	21.0	12.0
Brown, Chamberlain, and Te Linde <sup>14</sup>	335	36.8	43	28.2	14.9
Lardaro	147	30.0	63	13.0	6.4



### Summary and conclusion

One hundred fifty-seven consecutive abdominal myomectomies done from January, 1935, to January, 1958, are presented. In 66 cases where pregnancy was desired and

attempted, the success rate was 63½ per cent. The total fibroid recurrence rate was 13 per cent. Subsequent hysterectomy rate, after myomectomy, was 6.4 per cent.

A plea is made for the greater use of extensive myomectomy in selected cases.

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### Discussion

DR. ARTHUR M. DAVIDS, New York, New York. The members of the Gynecological Service of Mount Sinai Hospital have had a long and fruitful experience with the operation of myomectomy. As you have seen in Dr. Lardaro's Table I, Dr. Vineberg, in 1921, and Dr. I. C. Rubin, in 1942, presented papers on this subject from the service of the Mount Sinai Hospital. Since that time I have twice reported on our series of cases, once, in 1952, in the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY and again, in 1957, for the *Surgical Clinics of North America*. In the last publication, I presented the accumulated experience from 1921 to 1955. This consisted of 1,475 cases of myomectomy. Since that date another 275 cases have been performed, bringing our present series of cases to 1,750.

Dr. Lardaro quotes Dr. Victor Bonney as stating, in 1946, that there was a failing interest in the operation of myomectomy. This unfortunately was the case in some institutions, but even more unfortunate is the fact that an interest in radical myomectomy has never been aroused on the majority of surgical services. Over a period of approximately 10 years I have questioned the candidates for licensure by the National Boards on their final examination and have found that less than 10 per cent have ever seen a myomectomy performed during their medical school or hospital training. This lack of familiarity with the possibilities of radical myomectomy will surely deprive many women of the opportunity of a choice between hysterectomy or conservative uterine operation.

I must take issue with a few statements made in Dr. Lardaro's paper. The first is that myo-

mectomy "is time-consuming and unspectacular; it may be bloody and it is always fraught with danger." There is no more spectacular gynecological procedure than a radical myomectomy which converts a large fibroid uterus into one that can resume normal functions. Modern medical and surgical techniques have made myomectomy a safe procedure. Hemorrhage is no problem if a uterine tourniquet is properly applied. The excellent hemostasis obtained by the continuous application of the tourniquet gives the surgeon ample opportunity to work in an almost bloodless field. This reduces the operative time considerably and permits a more thorough procedure to be performed.

There are a few very definite differences of opinion as to the points in technique as outlined by Dr. Lardaro.

1. He states that the opening of the endometrial cavity was almost a routine procedure. The routine opening of the endometrial cavity has not been encouraged on the Mt. Sinai Service. A preoperative hystrogram and a routine curettage before myomectomy have eliminated entrance into the endometrial cavity except in those instances where pathology is detected within the cavity. The maintenance of an intact endometrial cavity will in many instances greatly influence the method of delivery in subsequent pregnancies. The obstetrician is much more inclined to attempt a vaginal delivery in the case in which the endometrial cavity has not been widely opened.

2. "When there are myomas in both uterine walls, first remove those on the anterior wall and then approach the posterior ones by the transcavity route." This is a procedure which we discourage except for the removal of a pedunculated fibroid arising from the posterior endometrial wall. In all other instances every effort is made to keep the endometrial walls intact so that normal implantation of pregnancy will occur and so that abnormal attachments, such as placenta accreta, are reduced to the minimum.

3. "Try to avoid posterior wall incision. Nearly all complications after myomectomy are the result of posterior wall incisions. . . ." Such fear of a posterior wall incision is completely unwarranted and may discourage the surgeon from performing a thorough removal of fibroids from the posterior uterine wall. We try to make the minimal number of incisions but when fibroids of the posterior wall are

present they are attacked in exactly the same manner as those occurring on the anterior wall of the uterus.

4. "On reconstructing the uterus, try to leave it only a little larger than normal." This idea is contrary to what we believe and to what we have practiced for the past 25 years. It is a hard and fast rule that none of the hypertrophied myometrium be sacrificed in the reconstruction of the uterus. When a radical myomectomy is performed on a fibroid uterus the size of a 4 to 6 months' gestation the reconstructed uterus may approximate the size of a 3 to 4 months' gestation. It is as illogical to sacrifice this myometrium as it would be to attempt to reduce the size of a term uterus after a cesarean section. The hypertrophied myometrium of the postmyomectomy uterus involutes in the course of 8 to 12 weeks and the uterus will return to normal size. The strength of the uterine wall in such a uterus will closely approximate that of the normal uterus. Uterine rupture has not occurred in any of our cases, and we believe that any removal of myometrium will increase the chance of rupture in subsequent pregnancy and labor.

In the Mount Sinai series, extending from 1921 to the present time, 1,750 myomectomies were performed. From 1921 to 1935, 225 were performed with a mortality rate of 4 per cent. In the period comparable to that of Dr. Lardaro's series, 1935 to 1958, 1,525 myomectomies were performed with one death in 1944 as a result of a pulmonary embolus. The mortality rate for this period has fallen sharply to 0.06 per cent. The postoperative morbidity has also sharply decreased as the results of the use of transfusions, antibiotics, and careful surgical technique.

In our series, 491 private patients were operated upon between 1945 and 1955. They were carefully followed, and of the 301 married patients 140 became pregnant and were delivered of 210 living children. There were 30 miscarriages out of a total of 240 pregnancies. The pregnancy rate was 46.5 per cent with an abortion rate of 12.5 per cent. The abortion rate in the preoperative group of 1,016 patients, ward and private, was 39.3 per cent. In our series, 48 patients have had myoectomies performed during pregnancy. The operations were performed mainly because of severe pain due to degenerative processes in the fibroid or due to greatly increased size of fibroids, producing

severe pressure symptoms. In 43 cases the operation was done before viability (6 to 20 weeks). Twenty-nine of these patients carried to term (67.3 per cent). The 5 patients operated upon after viability carried to term so that 72 per cent delivered term infants.

The recurrence rate following myomectomy depends upon many factors and is entirely unpredictable. The patient's age is one of the most important factors. When fibroids occur at an early age a special tendency to the formation of these tumors must be inferred. It is in these young women that the conservation of the uterus is most pressing. In our series 8 per cent of the women had recurrence of fibroids which produced symptoms requiring a second operative procedure.

DR. MORRIS A. GOLDBERGER, New York, New York. The uterine tourniquet, of course, was developed by Barreras, of Argentina, who thought it was original. I think it was Rubin who saw Barreras do it some 20 odd years ago and brought it to Mount Sinai Hospital. At first we also did as Dr. Lardaro recommended, opening the tourniquet every 10 to 15 minutes, but now we leave it on for over one hour with no ill effects. The tourniquet is introduced by incising the reflection of the bladder transversely, pushing it off the lower segment of the uterus below the cervix, and then passing a No. 8 French catheter, which is threaded on a galley needle, through the broad ligament about 0.5 cm. away from the uterine vessels going posteriorly, around anteriorly and through the left broad ligament, also 0.5 cm. lateral to the vessels, crossing the catheter in back, and putting a clamp on it. In that way a pretty good hemostasis is obtained. It is not complete, because the ovarian vessels haven't been controlled.

The type of abdominal incision is important. One must have adequate exposure. The uterus should be delivered entirely, if possible, outside the wound, for then a good survey as to what should be done is obtained, because if the tubal angles are not preserved, the purpose of this procedure is defeated. They must be preserved. Therefore, we always try to plan our incisions, whether they are on the anterior or the posterior wall, as near the midline as possible, and do all our subsequent removal of fibroids through these one or two incisions.

DR. J. RANDOLPH GEPFERT, New York, New York. I feel rather strongly that a curet-

tage should not be done immediately preceding myomectomy. It is a violation of aseptic and surgical principles to pass a curette through a potentially contaminated cervical canal into the uterine cavity when the possibility exists that this cavity will subsequently be entered through the sterile peritoneal cavity.

I also feel that the uterine cavity should always be entered during an intra-abdominal myomectomy. I have repeatedly seen postoperative hysterectomy specimens where the hysterectomy had been preceded by a thorough curettage, yet on opening the uterine cavity there were found submucous myomas and endometrial polyps which had not been touched by the curette. If the operative procedure of abdominal myomectomy is indicated, one should always enter the uterine cavity in order to be certain that additional pathology is not present. If curettage is indicated, it can better be carried out from above under direct vision. I have proved these points over and over again in patients on whom myomectomy was carried out as treatment for infertility.

I feel strongly that, if the uterine cavity is not contaminated from below, one need have no concern as to normal healing. As a matter of fact, it is frequently impossible to locate the line or lines of incision when they are looked for at subsequent cesarean section.

DR. E. W. MUNNELL, New York, New York. There are two things I should like to emphasize. Preliminary curettage is most advisable for deciding upon the technique of myomectomy, and the indications and the preparation for it.

Routine exploration of the uterine cavity is a debatable procedure, as we have heard tonight—one speaker being very much in favor of it, and the other discussor questioning its advisability. I think that the exploration of the uterine cavity should probably be done more often than it is, and not with any particular fear of subsequent rupture of the uterus during pregnancy. If done perhaps a little more often, it might remove from the list of failures of myomectomy those patients in whom an unrecognized submucous fibroid is responsible for a poor result.

DR. LARDARO (Closing). I have done a few posterior wall incisions. At times I have not been able to bring the bladder flap back as far as I would have preferred in order to peritonize completely. I like the hood operation in some

cases. I have done only five, and have observed the results in two at subsequent operations—one at cesarean section, and the other at hysterectomy. It is surprising how that posterior flap of the uterus fuses with the rest of the uterus. In this operation the end result is a vertical incision under a transverse one—a safeguard against possible rupture.

It is difficult to decide whether to do a section after a myomectomy. The figures show that rupture occurs in one patient in 60 al-

lowed to go into active labor. This is one too many. The decision may be somewhat influenced by the extent of the myomectomy, the postoperative reaction, and, of course, the conditions at the onset of labor.

In reference to Dr. Gepfert's comment, it may be noted that Dr. Bonney did not do any curettages. He opened the endometrial cavity, and he curetted from above with the back of the knife. I wonder whether when we open the endometrium we are doing much harm to the uterus.



# Posterior colpotomy: an avenue for definitive pelvic operations

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THE vaginal approach to pelvic lesions has long been accepted as an excellent surgical technique. Vaginal hysterectomy has been enthusiastically adopted by gynecologists and surgeons throughout the world. More recently, the culdoscope has been employed extensively as a diagnostic tool, and many reports attest to the efficacy of the instrument.<sup>1-5</sup> Many unnecessary exploratory laparotomies have been avoided as a result. Colpotomy, however, has been less enthusiastically accepted by most gynecologists, although occasional authors<sup>6-15</sup> have intermittently reported on the technique as a means of exploring the pelvic contents, but definitive surgical procedures have then been reserved for the abdominal route after diagnosis.

Posterior colpotomy with complementary surgical procedures has been reported even less frequently.<sup>16, 17</sup> Critics argue that the exposure afforded is inadequate, the operation technically difficult, and the approach fraught with potential sepsis.

Recently, the senior author<sup>18</sup> reported on 81 patients subjected to posterior colpotomy for diagnosis, and, where possible, definitive procedures at Fitzsimons Army Hospital and Colorado General Hospital. Of these patients, 34 were operated upon at Fitzsimons Army Hospital during the 2 year period, 1955-1957. The favorable results obtained, the low incidence of significant complications, and further experience with the operative technique lead us to the present report.

## Material

During the period Jan. 1, 1955, to Dec. 31, 1958, the pelvic lesions in 100 patients were approached surgically through the posterior colpotomy incision at Fitzsimons Army Hospital. Major gynecologic procedures were performed on 502 patients during this interval of time. Thus, one out of every 5 patients requiring major gynecologic operations was selected for a posterior colpotomy. The resident staff, in various stages of their training, performed most of these surgical procedures.

## Operative technique

The techniques described by Bradbury,<sup>14</sup> Doyle,<sup>12</sup> and Daly<sup>15</sup> are utilized. With the patient under satisfactory anesthesia and in the lithotomy position, the vagina is prepared with hexachlorophene (pHisohex) and the bladder emptied. A weighted speculum is placed in the vagina and the posterior lip of the cervix is grasped with a toothed tenaculum and traction is maintained in the direction of the symphysis pubis. The vaginal mucosa is grasped posteriorly in the midline, 2 to 3 cm. below the cervix, between the insertion of the uterosacral ligaments (Fig. 1). A transverse incision is made through the vaginal mucosa and the mucosa is undermined laterally with scissors, separating the mucosa from the underlying fascia. The peritoneum is then identified and incised (Fig. 2). Bleeding is usually minimal and easily controlled. Division of the uterosacral ligaments and the

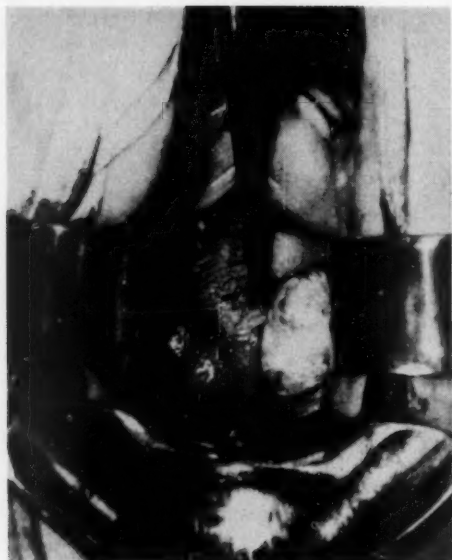


**Fig. 1.** Weighted speculum positioned, posterior lip of cervix grasped in midline posteriorly.

**Fig. 2.** Vaginal mucosa opened transversely, exposing underlying fascia and peritoneum. Peritoneum grasped with forceps in midline.

**Fig. 3.** Weighted speculum and narrow Dever retractors positioned within operative site, exposing posterior surface of uterus.

**Fig. 4.** Right ovary exposed.



**Fig. 5.** Left ovary, tube, and parovarian cyst exposed.



**Fig. 6.** Corpus luteum cyst, 5 cm. in diameter, exposed.

Schuchardt perineotomy are rarely necessary for adequate exposure, but the former affords good exposure when needed. Narrow Dever retractors are positioned for exposure, and the weighted speculum repositioned within the cul-de-sac (Fig. 3). Direct visualization of the pelvic structures is facilitated by grasping the suspensory ligaments of the ovaries with a Babcock clamp. Fundal pressure will aid in rotating the uterus posteriorly. The use of a uterine sound has been advocated to effect such retrodisplacement but has proved unsatisfactory in our hands. Grasping the posterior wall of the fundus with a toothed instrument should be avoided. The ovary can be held with a ring forceps or Babcock clamp if necessary. No instrumentation of the tubes is necessary for exploration for they are readily seen when the ovary is brought down into the operative field. The Trendelenburg position will usually displace the intestines out of the operative field, but a gauze pack may be used if necessary. Salpingectomy, tubal ligation, wedge resection, oophorocystectomy, and oophorectomy can then be performed without difficulty in suitable candidates (Figs. 4-9). Closure of the colpotomy incision in

one layer with chromic catgut, with or without Penrose drains, completes the procedure. An indwelling Foley catheter is rarely necessary. A 2 inch vaginal pack for pressure



**Fig. 7.** Pomeroy sterilization. Chromic suture ligation about knuckle of tube held with Babcock clamp. Suspensory ligament of ovary similarly held.

hemostasis is used and removed 8 hours later. Anterior colpotomy<sup>16, 23</sup> and the knee-chest position for the posterior approach<sup>15</sup> were not used in this series.

### Indications

Posterior colpotomy is indicated for both diagnostic and surgical procedures in suitable candidates. Suitability is a matter of judgment and experience, and it is obvious that proficiency with the technique broadens the indications. Ideally, the exploratory

colpotomy replaces the exploratory laparotomy in most gynecologic patients. Many indications parallel those reported for culdoscopy,<sup>5</sup> namely, (1) emergency conditions which include acute problems requiring differential diagnosis between extrauterine pregnancy and adnexal disease; (2) problem cases with chronic symptomatology where pelvic disease is suspected but unproved; (3) pelvic masses; (4) suspected endocrinopathies, particularly the Stein-Leventhal syndrome. Eligibility will also include (1)



Fig. 8. Ovarian mass, 6 cm. in diameter, exposed—a thecoma.

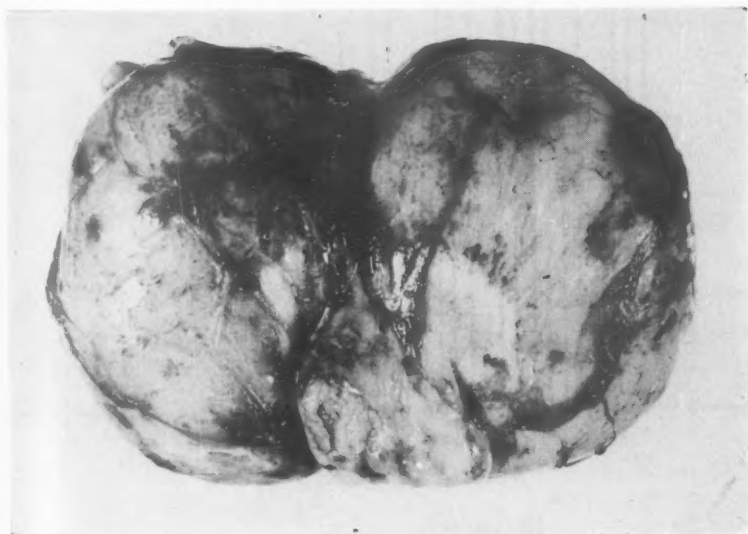


Fig. 9. Ovarian mass, 6 cm. in diameter—a thecoma—removed by posterior colpotomy. Tumor has been sectioned.



sterilization and castration candidates; (2) patients with cul-de-sac abscess and hematomas; (3) young women with essential dysmenorrhea suitable for paracervical uterine denervation as advocated by Doyle.<sup>19</sup>

A definitive procedure through the colpotomy incision is possible on all accessible lesions. However, there are certain definite limitations and contraindications. These include: (1) inability to deliver successfully most adnexal masses greater than 6 cm. through the colpotomy incision without rupture or decompression; (2) a fixed cul-de-sac

mass; (3) acute pelvic inflammation; (4) acute hemoperitoneum. Nulliparity and previous abdominal or vaginal operation rarely contraindicates the approach. A tendency to perform surgical gymnastics should be avoided and laparotomy selected when colpotomy exploration reveals extensive disease or malignancy. Failed colpotomy as with failed forceps should carry no stigmas in the surgeon's mind. Minimal blood loss and prolongation of anesthesia accompany exploration, closure, and repositioning of the patient for laparotomy.

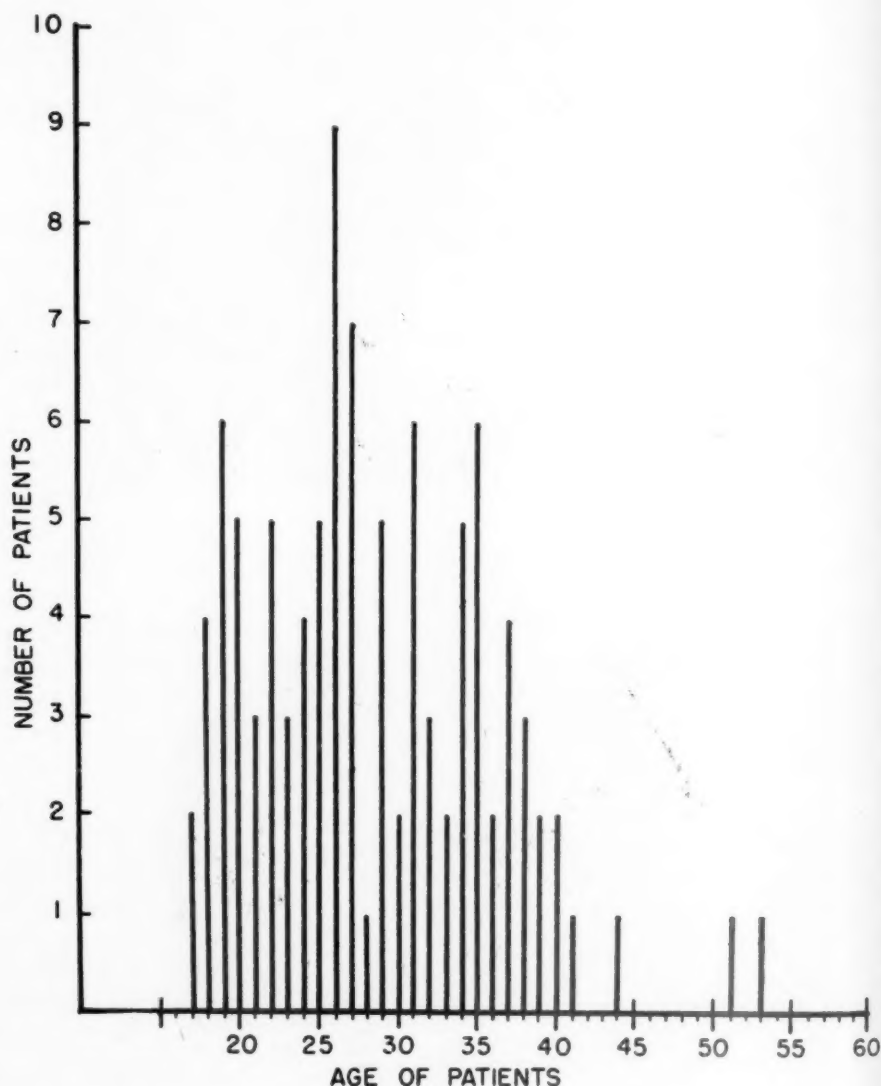


Fig. 10. Age distribution of 100 patients.

### Analysis of material

**Miscellaneous.** The average age of the patients in this series was 28. The youngest patient was 17, the oldest 53. Almost all were within the childbearing period (Fig. 10). Thirty-six of the patients were nulliparas, 24 were primiparas, and the remaining 40 were secundigravidas or better. Seven patients were Negroes, and the others white. A general anesthetic agent, usually Pentothal and nitrous oxide, with or without endotracheal intubation, was used 95 times. Spinal anesthesia was used 4 times, and, in one instance, a large cul-de-sac hematoma was drained 4 days postoperatively under trichlorethylene (Trilene) analgesia. Approximately one third of all patients had had previous major abdominal or gynecologic operations. The posterior colpotomy was repeated in 2 patients without undue difficulty, morbidity, or complication. The average duration of hospitalization was 3.7 days in contrast to the usual 7.9 days required for major abdominal or gynecologic procedures.

**Preoperative symptoms and findings.** More than one half of the patients in whom the approach was through the cul-de-sac complained of pain and had a palpable adnexal or pelvic mass (Table I). Patients suspected

Table I. Preoperative symptoms and findings

Pain	54
Mass	58
Infertility	7
Dysmenorrhea	4
Endocrinopathy	8
Other	19
Sterilization	13
Complementary	4
Castration	2

of having acute inflammatory disease were not selected for colpotomy unless a cul-de-sac mass persisted after conservative management. Four patients presented a large pelvic mass compatible with a pelvic hematoma after panhysterectomy. Approximately one fifth of the patients were asymptomatic and the posterior colpotomy approach was utilized for a Pomeroy type sterilization,

castration for carcinoma of the breasts with metastasis, and for exploratory purposes to complement vaginal plastic repair procedures.

Other presenting symptoms leading to a colpotomy were endocrine dysfunction, severe essential type dysmenorrhea, and, rarely, infertility.

**Preoperative diagnosis.** Ectopic pregnancy was suspected in almost one third of the cases, 28 per cent and was confirmed in 9

Table II. Preoperative diagnoses

Ectopic pregnancy	28
Cyst or mass	17
Pelvic inflammatory disease	7
Abscess-hematoma	11
Endocrinopathy	9
Dysmenorrhea, essential	4
Sterilization candidate	13
Endometriosis	4
Miscellaneous*	7

\*Symptomatic pelvic relaxation, 3; pain, cause undetermined, 1; breast cancer, 2; postoperative colporrhagia, 1.

per cent (Table II). Colpocentesis was performed in 21 of the 28 patients, and in 9 patients a positive tap was obtained. In 3 patients, the tap was equivocal, and in the remaining 9 patients a negative tap was reported. Unfortunately, our results with colpocentesis parallel those reported by others as 3 of the 9 patients with positive taps had no disease and 3 of the 9 with negative taps did have an ectopic pregnancy, one associated with a significant hemoperitoneum.

Suspected ectopic pregnancy, a pelvic adnexal cyst or mass, and pelvic inflammatory disease comprised the majority of preoperative impressions—63 per cent in this series. These primary impressions were confirmed in 53 per cent of the patients.

**Postoperative diagnosis.** The most frequent findings at colpotomy were ectopic pregnancy, adnexal disease, and a cul-de-sac mass or abscess. These comprised 45 per cent of the pelvic findings. As expected, 40 per cent of the patients had essentially normal pelvis (Table III). This is under-

Table III. Postoperative diagnoses

Ectopic pregnancy		9
Tubal	7	
Cornual	1	
Ovarian	1	
Functional cyst		17
Ovarian tumor		7
Dermoid	4	
Thecoma	1	
Serous cyst	1	
Pseudomucinous cyst	1	
Leiomyoma		2
Pelvic inflammatory disease		6
Abscess-hematoma		12
Stein-Leventhal syndrome		5
Endometriosis		2
Normal pelvis		40
Total		100

standable, as 24 per cent of the patients were expected to have a normal pelvis and were subjected to colpotomy for purposes of sterilization, castration, and resection of the uterosacral nerve plexus.

Seven ectopic pregnancies were tubal, and 6 of these were associated with hemoperitoneum. Two other ectopic pregnancies, one ovarian and one cornual, were easily visualized through the colpotomy incision.

Discrete adnexal lesions were visualized in 29 per cent of the patients. Seventeen per cent of these were functional ovarian cysts, usually corpora lutea. Such cysts, with or without pregnancy, and with associated menstrual irregularities, were most often confused with ectopic pregnancy. A differential diagnosis was easily made through the cul-de-sac.

**Procedures performed.** Posterior colpotomy was successfully performed 95 times and was unsuccessful in 5 instances (Table IV). We do not consider the procedure a failure when exploration reveals extensive disease better handled abdominally. However, failure to enter the cul-de-sac or complete the surgical procedure initiated does represent an unsuccessful result. Only one failure resulted in a significant complication; this is reviewed (Case 5).

Exploration, in some cases with associated vaginal plastic operation, was performed upon one quarter of the patients. Salpingec-

tomy, oophorocystectomy, oophorectomy, and vaginal drainage of cul-de-sac masses comprised the majority of definitive procedures performed.

The colpotomy approach was used for all sterilizations during this 3 year period, except for sterilizations at the time of cesarean section, as advocated by Allen<sup>16</sup> and Boysen.<sup>17</sup> The Pomeroy technique was utilized not sooner than 6 weeks post partum. In 4 instances, therapeutic abortion was also performed, preferably *after* sterilization so as to avoid, at least on theoretical grounds, the intrapelvic implantation of viable endometrial cells.

Table IV. Operation performed

Colpotomy successful		95
Exploratory only		23
Salpingectomy		21
Pomeroy	13	
Ectopic	7	
Pelvic inflammatory disease	1	
Oophorocystectomy		14
Oophorectomy		8
Drainage		13
Doyle procedure		4
Wedge resection		5
Miscellaneous*		7
Colpotomy failure		5
Total		100

\*Associated vaginoplastic, 3; biopsy rectovaginal septum, 1; enterolysis, 1; salpingoplasty, 1; cervicectomy, 1.

Paracervical uterine denervation by transection of the uterosacral ligaments with reattachment of these structures after interposition of the peritoneum, as advocated by Doyle,<sup>19</sup> was performed 5 times, once in association with a Pomeroy operation and a hysteropexy. Two additional cases have been similarly treated through the abdominal route. It is of interest that excellent results have been obtained to date with this technique which is more easily accomplished than a presacral neurectomy.<sup>20</sup>

Various authors, notably Stein and Leventhal,<sup>21, 22</sup> have emphasized that exploratory laparotomy is rarely necessary when the Stein-Leventhal syndrome is suspected. The use of pneumogynecography and culdoscopy has been advocated for diagnosis, and

laparotomy is resorted to for wedge resection. Wedge resection of large polycystic ovaries in 5 cases was accomplished with posterior colpotomy as these large ovaries were often dependent, prolapsed in the cul-de-sac, and easily approached.

**Complications and limitations.** There were no deaths attributable to posterior colpotomy in this series. Colpotomy was unsuccessful in 5 instances and laparotomy was required after failure to enter the cul-de-sac in 2 cases; in the 3 other cases technical difficulties indicated the abdominal approach, and the colpotomy was abandoned. There were 5 complications directly attributable to the procedure itself, in 3 instances with associated morbidity. All 5 cases required some degree of extension of hospitalization. These complications are reviewed briefly.

#### Case reports

**Case 1.** Mrs. K. L., a 24-year-old nullipara, was admitted with an early incomplete abortion with sepsis. Pelvic examination revealed an 8 to 10 cm. mass in the cul-de-sac. A positive colpocentesis was obtained. Ectopic pregnancy was diagnosed and exploration was done through the cul-de-sac. A 10 cm. blood-filled cystic mass was identified, apparently a "tubal abortion." The operator elected to remove the mass vaginally. The cystic mass was ruptured and could not be removed. Laparotomy was performed after closure of the colpotomy incision and a left salpingectomy done without difficulty. Total operating time was 1 hour, 22 minutes. Postoperatively, the patient had 4 days of morbidity. The colpotomy incision was reopened, and 200 c.c. of old blood drained. *Staphylococcus aureus* was cultured. The subsequent postoperative course was uneventful.

**Case 2.** Mrs. W. D., a 27-year-old primipara, was admitted with acute abdominal pain. A right adnexal mass, 6 cm. in diameter, was palpated. Colpocentesis was negative. Ectopic pregnancy was diagnosed and the patient scheduled for operation. Colpotomy revealed considerable hemoperitoneum and a ruptured ectopic pregnancy replaced most of the right tube. Salpingectomy was performed without difficulty. The incision was closed without drainage. The immediate postoperative course was uneventful. She was discharged 5 days post-

operatively and returned 11 days later, febrile, with a large cul-de-sac abscess which was drained. *Escherichia coli* was cultured. The subsequent postoperative course was unremarkable.

**Case 3.** Mrs. O. E., a 22-year-old nulligravida, was admitted complaining of intermittent lower abdominal pain. A 4 cm. firm mass was palpated in the right ovary. A dermoid cyst was diagnosed and a posterior colpotomy done. A cystic right ovary was identified and the preoperative impression confirmed. The cyst was inadvertently ruptured with delivery but oophorocystectomy was accomplished without further difficulty. The postoperative course was benign. Five days later she was admitted to a hospital in Kansas with clinical findings suggestive of peritonitis. She responded to conservative treatment but continued to complain of lower abdominal pain, dyspareunia, and irregular and painful menses. Two laparotomies were performed by different doctors in Kansas with enterolysis of multiple abdominal pelvic adhesions as well as a left salpingo-oophorectomy and a ventral suspension. She continued symptomatic and was readmitted to the hospital in October, 1958. Laparotomy revealed extensive pelvic adhesions, hydrosalpinx, and an atrophic right ovary. A panhysterectomy and right salpingo-oophorectomy were performed without difficulty. She has remained asymptomatic since.

**Case 4.** Mrs. A. H., a 40-year-old primipara, was admitted with a 6 cm. right adnexal mass. Dermoid cyst was diagnosed. Colpotomy was performed and a right oophorectomy done for the dermoid cyst without difficulty. She was discharged 4 days later and then readmitted the next week, at which time she was febrile, complaining of lower abdominal pain. A right adnexal mass was palpated and was felt to represent a retroperitoneal hematoma. The patient responded to conservative treatment and the mass gradually resolved.

**Case 5.** Mrs. M. N., a 37-year-old primipara, was admitted complaining of infertility, chronic pelvic pain, dysmenorrhea, and dyspareunia. Despite the presence of a fixed pelvic mass, colpotomy was attempted. The cul-de-sac could not be entered and extraperitoneal perforation of the rectum resulted. The operator repaired the defect and at the insistence of the general surgery staff, performed a diverting colostomy. Pelvic exploration was deferred. The colostomy was subsequently closed and another laparotomy performed in October, 1958, which revealed ex-



tensive pelvic endometriosis, multiple myomas, and adhesions. A panhysterectomy and left salpingo-oophorectomy were accomplished and the patient has done well since.

These 5 cases illustrate several of the limitations and complications associated with the surgical technique. As a consequence, we believe that (1) this approach is not indicated in the presence of adnexal masses greater than 6 cm. in diameter; (2) Penrose drainage of the cul-de-sac is advisable when hemoperitoneum is encountered; (3) a fixed pelvic or cul-de-sac mass will usually contraindicate posterior colpotomy as the probability of injury to the rectum is enhanced (diverting colostomy is probably not necessary when the rectum is perforated and would not be used again under similar circumstances); (4) rupture of an ovarian cyst is more likely with posterior colpotomy than with laparotomy—a definite threat when pseudomucinous cystadenoma or cystic teratoma is recognized. It is of interest that 25 per cent of all ovarian cysts were inadvertently ruptured when delivered through the colpotomy incision.

In 5 additional cases, definitive procedures were performed successfully through the cul-de-sac with considerable difficulty. Operations performed included enterolysis and salpingectomy for extensive pelvic inflammatory disease, cornual resection of an unruptured ectopic pregnancy, salpingoplasty, and catheter decompression with subsequent oophorectomy of a 15 cm. pseudomucinous cystadenoma. In another instance, successful performance of a Pomeroy sterilization in a patient with cirrhosis required a Schu-

hardt perineotomy and division of the uterosacral ligaments for adequate exposure. Surgical gymnastics such as these are to be avoided and failure of the procedure readily admitted before trouble arises.

### Conclusions

Posterior colpotomy is an excellent surgical technique which has not been afforded its proper merit in the gynecologic literature. Exploratory laparotomies for suspected pelvic conditions can be supplanted in most instances by the vaginal approach provided certain contraindications and limitations are recognized. While we do not use the culdoscope at Fitzsimons Army Hospital, recent reports attest to its efficacy as a "valuable diagnostic aid with a low failure rate, minimal complications, and no mortality."<sup>5</sup> We believe posterior colpotomy has the added advantage of permitting definitive procedures in many cases after diagnosis, without considerable repositioning from the modified knee-chest positions described. However, we agree that the 2 procedures should not be considered competitive. Each has its place and the method suiting the operator best should be used whenever possible.

### Summary

A review of 100 consecutive posterior colpotomies performed at Fitzsimons Army Hospital from January, 1956, to December, 1958, has been presented. The surgical technique, indications, contraindications, and limitations have been outlined. Posterior colpotomy has proved a useful surgical avenue of approach to pelvic lesions.

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# Bloodless technique of cold knife conization (ring biopsy)

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IT HAS long been recognized that excessive blood loss is a frequent accompaniment of adequate cold knife conization (ring biopsy) of the cervix, done primarily to confirm a preclinical or a preinvasive carcinoma of the cervix as suspected by doubtful or positive cytology. Many techniques have been developed in an attempt to control the blood loss.

In 1815, Lisfranc,<sup>1</sup> during the treatment of a suspected cervical carcinoma, removed a wedge-shaped portion of the cervix for diagnosis. He suggested, at that time, that the portion of the cervix to be removed extend from the vagina to the margin of the internal os. Emmett,<sup>2</sup> in 1874, reported Hughier and Marion Sims had also performed a similar operation for diagnosis of cervical carcinoma. In 1916, Sturmdorf<sup>3</sup> described conization followed by inversion of flaps of mucosa over the bare areas with the use of sutures for hemostasis. In 1928, Hyams<sup>4</sup> introduced electroconization for cervicitis. In 1948, Ayre<sup>5</sup> developed a special knife in order to obtain a more complete ring- or cone-shaped specimen with greater ease. In 1949, Gusberg<sup>6</sup> produced the endocervical coning biopsy curette which was probably the first of the specialized instruments for cold conization of the cervix. Since then there have been many articles<sup>7-9</sup> pub-

lished showing specialized instruments which were designed to control hemorrhage and facilitate the operation. In 1951, at a seminar on ring biopsy at The Cancer Institute in Miami, it was suggested that the blood loss could be decreased by injection of the cervix with Novocain and Adrenalin prior to the operation. Ring biopsy is usually considered a minor surgical procedure. However, a study by Boyd<sup>10</sup> of the morbidity and complications of 80 cases of Sturmdorf's conization reveals a 43.4 per cent complication rate (Table I).

Table I. Complications in 80 cases of Sturmdorf's conization

Febrile response (over 99.6° F.)	
Without other complications	18
With other complications	10
Bleeding requiring repacking	7
Bleeding requiring repacking and resuturing	5
Bleeding requiring hysterectomy*	1
Accidents during operation	1
Marked infection of the uterus	1
Interference with pregnancy	2

\*The patient who required hysterectomy was hospitalized 38 days and was given transfusions totaling 5,000 ml. of blood.

Cold knife conization is a prime diagnostic method and is considered necessary in the accurate diagnosis of early preclinical carcinoma. Four quadrant biopsies have proved difficult to interpret or misleading in

*Presented in movie form before The Pan American Cytology Congress, Miami, Florida, April, 1957.*

45.5 per cent of 110 cases as reported by Harris and Peterson.<sup>11</sup>

### Technique

An improved simplified bloodless technique\* of ring biopsy has been developed in which the average blood loss can be decreased from 200 ml. to less than 5 ml. This method is so simple, easy, and safe that it can be, and has been, used in all trimesters of pregnancy, without a single pregnancy loss. The procedure is ordinarily done in the hospital under Pentothal-Nitrous oxide anesthesia. Lugol's solution for a Schiller test is applied to the cervix and the vagina to delineate properly the margin of nonstaining, abnormal tissue to be removed (Fig. 1). If the entire portion of the cervix stains well, as it does in a few cases of carcinoma, then at least all tissue 1.5 cm. from the squamocolumnar junction should be removed for biopsy. The cervix is brought into view with 2 tenacula, placed at 3 and 9 o'clock. Great care is used not to disturb the epithelium at the squamocolumnar junction. The key to this technique lies in the production of an *intracervical tourniquet* by injection into the cervical stroma of sterile saline to which 3 drops of Adrenalin per ounce has been added (Figs. 2 and 3). The injection is made far away from the squamocolumnar junction, actually around the circumference of the cervix close to the vaginal fornix at 6 or 8 points. Enough solution (50 to 200 ml.) is injected to produce ballooning and blanching of the entire cervix (Fig. 3). If enough solution is not injected to produce this blanching and ballooning effect, the entire technique will be a failure. It is of extreme importance that the injection be made within the *cervical stroma*, not submucosally (inset, Fig. 2). This requires great force, necessitating the use of a control syringe with finger rings and a 2 inch, 20 gauge needle bent to a 45 degree angle (Fig. 2). Following the injection, a cone of tissue

\*This technique was developed by us in 1951; subsequently, we have discovered that a similar technique without cauterization has been used by Cary Hiatt<sup>12</sup> of Fort Worth, Texas, and J. M. Singleton<sup>13</sup> of Kansas City, Mo.

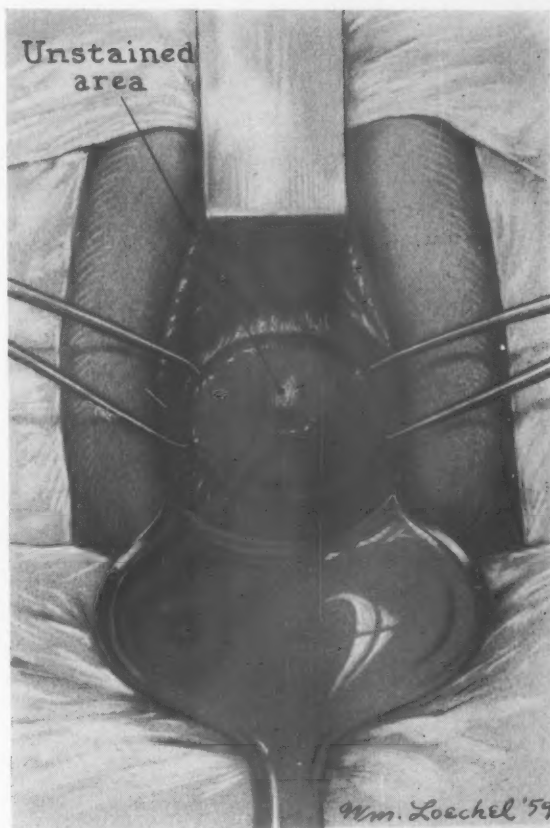


Fig. 1. Cervix stained with Lugol solution before injection.

is removed, including a portion well beyond the nonstaining area plus at least two thirds of the cervical canal (Fig. 4). A No. 11 Bard-Parker blade with an angled handle can be used. It is extremely important that the knife point extend to the endocervical canal but not through to the opposite side, in order to prevent undercutting, which can lead to troublesome bleeding. If the injection is properly made, the biopsy site will show no bleeding. The entire raw area is then coagulated with a Bovie unit for subsequent hemostasis. If the coagulation is not done within 15 minutes, the area usually bleeds profusely. The entire blood loss, if the injection technique has been properly followed, is not more than 5 ml., and an entirely dry field should be obtained. Following the conization, if the patient is not pregnant, the cervix is dilated and a routine fractional curettage is done. Then, a pledget of Oxycel



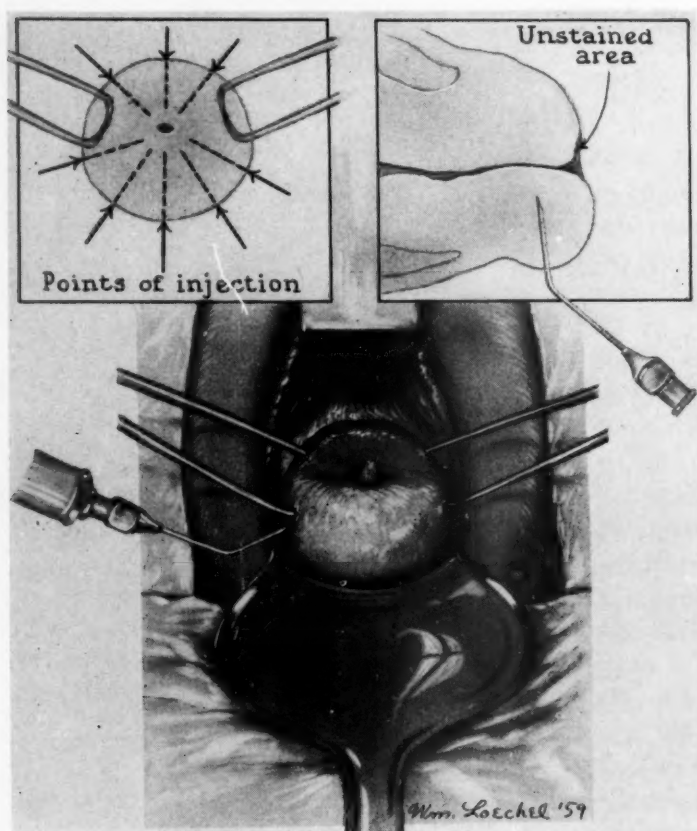


Fig. 2. Ballooning and blanching effect and sites of injection.

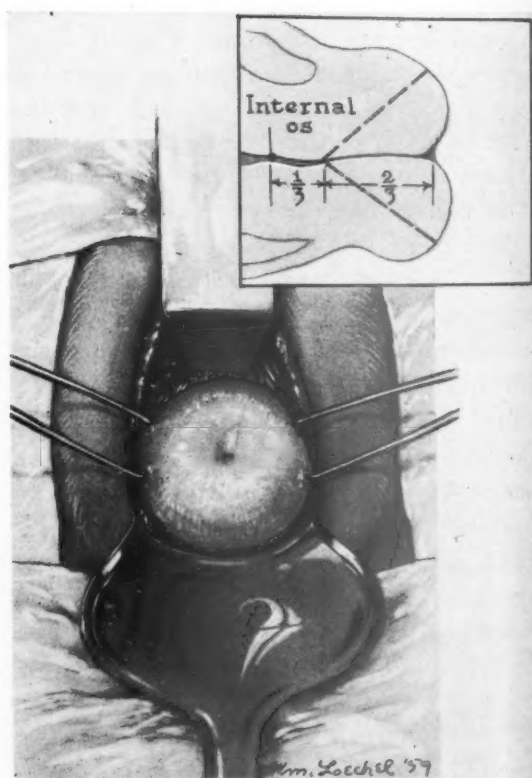


Fig. 3. Injection completed. Inset shows cone of cervix to be removed.

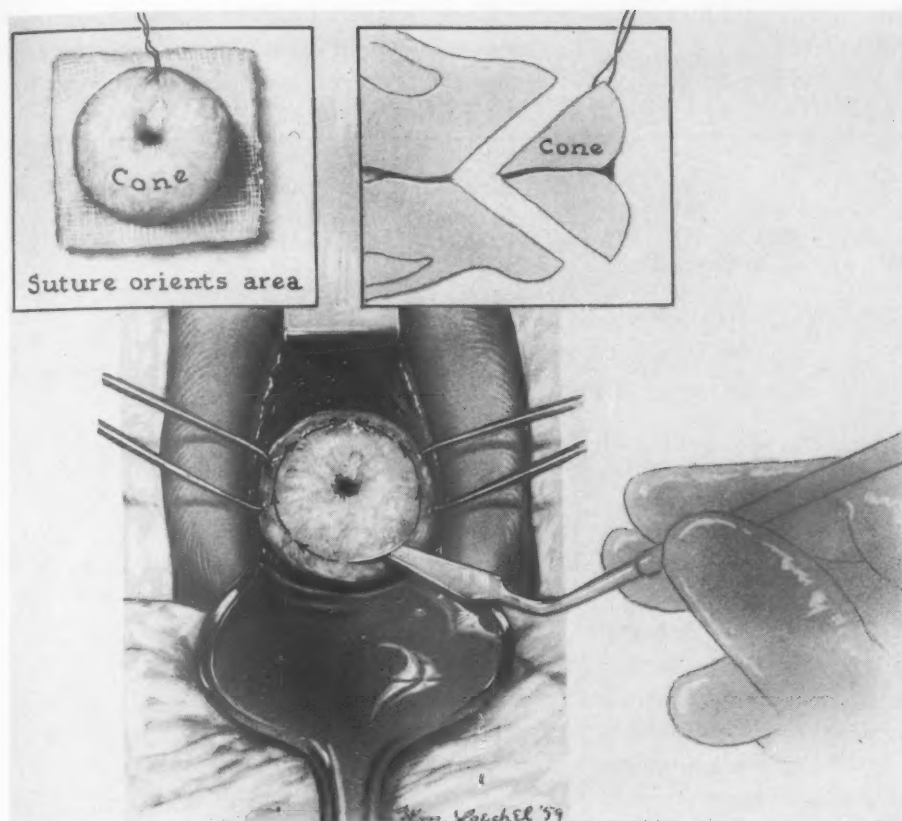


Fig. 4. Line of incision and orienting suture at 12 o'clock.

cotton is placed against the cervix with pressure for a moment or two and allowed to remain. No packs or sutures are required.

#### Complications and morbidity

All 88 patients in our series returned home within 48 hours following operation unless definitive therapy was contemplated on the same hospital admission. None was rehospitalized for complications (Table II).

Table II

Postoperative hemorrhage* (9.7 per cent)	9
Cystitis	1
Acute perisalpingitis†	1
Pyelonephritis, parametritis, and ovarian abscess	1

\*Hemorrhage occurred on the second to the twenty-fourth postoperative day; this was controlled either in the office or in the emergency room at the hospital by recauterization and the placing of Oxycel against the cervix.

†This was discovered at the time of follow-up operation for an early invasive carcinoma.

These patients are discharged on the first or second postoperative day and instructed to use an ointment composed of allantoin and sulfanilamide (Allantomide Vaginal Cream) nightly to minimize secondary slough. Unless the uterus is removed for definitive therapy later, the cervix is periodically dilated to prevent cervical stenosis.

Of these 88 patients, 2 have had 2 pregnancies without prolonged labor or other difficulties attributable to the conization. Two had cesarean hysterectomy for definitive therapy, and one had cesarean section for cephalopelvic disproportion.

#### Summary

A bloodless technique of cold knife conization to confirm preclinical or preinvasive carcinoma of the cervix is presented.

An intracervical tourniquet is produced by injection of the cervical stroma with

saline Adrenalin solution followed by coagulation of the coned area.

Eighty-eight cases are reported with 9.7 per cent minor postoperative hemorrhage and 2.9 per cent postoperative infection.

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# Construction of a functional vagina

A new surgical approach in congenital absence of the vagina

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CONGENITAL absence of the vagina fortunately is a rare anomaly, with considerable variation in incidence in different parts of the world. The rarity of the condition is inversely proportional to the variety of measures attempted for its repair. Most of the surgical methods<sup>1-14</sup> previously used entail construction of a canal in the rectovesical space, where the normal vagina should have developed, and then providing this canal with a lining of a suitable material obtained from another part of the body.

The purpose of this communication is to present a new approach that simulates the normal embryologic development and to describe its application in 4 cases. It is also suggested that the term "artificial vagina" should be replaced by "functional vagina" in describing the operation for congenital absence.

The procedure, which consists of a preliminary abdominal stage followed by a perineal operation, aims to accomplish the following objectives: (1) establishment of a fixation point for the superior support of the future vagina, and (2) establishment of adequate space for the formation of the new vaginal canal in a longitudinal plane.

## Embryologic development

A short review of the formation of the female genitals in the embryo is apropos as orientation for the principles of the surgical

procedure. The Müllerian (paramesonephric) duct (the primordial structures from which uterus, tubes, and vagina arise) first appears during the latter part of the second month close beside the mesonephric (Wolfian) ducts. The Müllerian ducts arise independently by a process of infolding and subsequent closing off of a groove in the celomic mesothelium parallel to the mesonephric duct. The distal ends of these ducts fuse together and form a Müllerian tubercle which is projected into the lumen of the urogenital sinus. Later, this tubercle opens up to establish the vaginal orifice marked by the hymen. The originally deep and narrow urogenital sinus becomes wider and shallower to form the so-called vestibule. This change brings the vaginal orifice into its definitive position, much nearer the surface than it was in earlier stages. The uterus, cervix, and upper part of the vagina are formed from the fused caudal ends of the Müllerian ducts. The part of the Müllerian duct between the uterus and the ovary on each side forms the uterine tubes.

## Clinical findings

Our 4 cases presented practically identical clinical features with respect to history, physical development, and genital abnormalities coinciding with absence of the vagina. Patients' ages ranged from 17 to 28 years. All had the same presenting complaint, i.e., absence of menstruation. Findings in Case 1 were typical for all 4 patients.

*From Lakewood Hospital.*



**Case 1.** Appearance and configuration of the 17-year-old girl were definitely feminine. Breasts were well developed, pubic hair was present with feminine distribution, and mons pubis and vulva appeared normal. All secondary female sexual characteristics were fully developed. Between the labia minora, the urethral opening was in its proper location, but immediately posterior to the urethra there was a tiny portion of mucous membrane, about 1 cm. in diameter, without any orifice. Rectal examination revealed absence of the vagina. Both ovaries were normal in size and consistency and could be palpated easily. Movement of the finger within the rectum toward the potential vaginal space revealed that there was very little tissue between this site and the peritoneal reflection internally.

All 4 patients were anxious for surgical correction of the anomaly, which caused them considerable emotional anxiety. They all wanted to rid themselves of "feeling like a freak," but were fearful that any surgical device would be "artificial." All the patients were extremely sensitive about the anomaly and the emotional distress it caused, and did not wish to discuss it with anyone. Normal sexual urges and desire for marriage were strong even though the patients realized that

childbearing would be impossible. Two patients were actually engaged to be married at the time of consultation. They wanted reassurance that a sexually satisfactory marriage would be possible before revealing the details about the anomaly to their prospective husbands.

The prospect of a normal sexual life, plus the gratifying emotional reassurance resulting from acquisition of an organ that was missing congenitally are sufficient indications for construction of a *functional* vagina and avoidance of the term "artificial" with its connotation of abnormality.

#### Surgical findings and technique

The *first stage* consists of laparotomy to visualize the anatomy and evaluate the development or underdevelopment of the paired embryologic Müllerian duct remnants and to determine the space between the perineum and pelvic peritoneal cavity (Fig. 1). Then the abnormalities are corrected by mimicking, as nearly as possible, the normal embryologic development, as a basis for later construction of the new vagina.

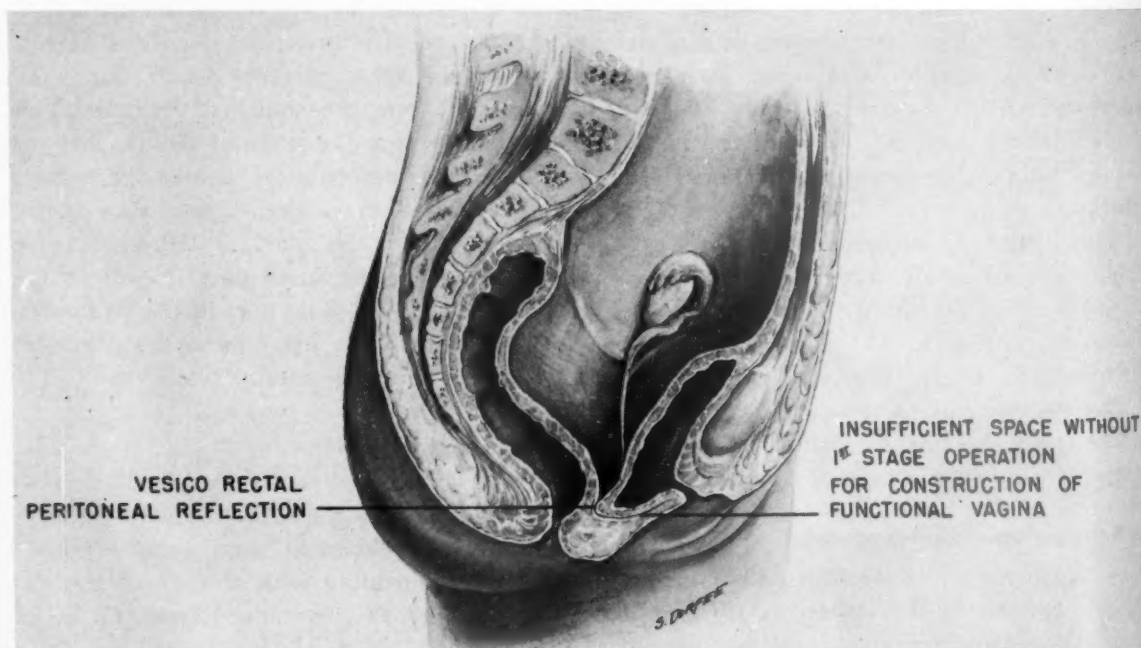


Fig. 1. Usually there is a relative lack of depth between vesicorectal peritoneal reflection and external surface.

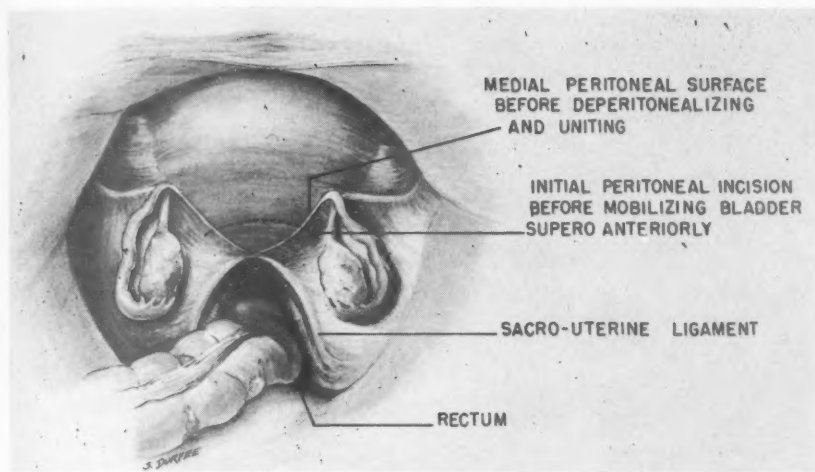


Fig. 2. Usual appearance of pelvic cavity and line of incision to mobilize bladder.

With the patient in the lithotomy position, a Pfannenstiell incision is made in the abdomen. The two Müllerian remnants are identified on each side. These course separately, inferiorly, anteriorly, and medially toward the normal position of the cervix to a retroperitoneal space in the inferior portion of the rectovesical peritoneal reflection between the bladder and the rectum. Each uterosacral ligament is visualized distinctly running superiorly, medially, and anteriorly fixing its distal ends to this site. Each Müllerian remnant is approximately 1.6 cm. in diameter and becomes increasingly narrower as it extends inferiorly (Fig. 2).

With the finger of an assistant pressing against the normal site of the vaginal orifice and the examining finger of the operator at the inferior peritoneal reflection, space between the external surface and the inferior peritoneal reflection (about 1 to 2 cm.) is easily determined. The transverse incision in the peritoneum is then made just anterior to the inferior pole of the area where the Müllerian remnants unite. This is opened transversely for approximately 4 to 5 cm. The urinary bladder is then mobilized superiorly and anteriorly, thus leaving the endopelvic fascia exposed. The medial portion of each Müllerian remnant is then deperi-

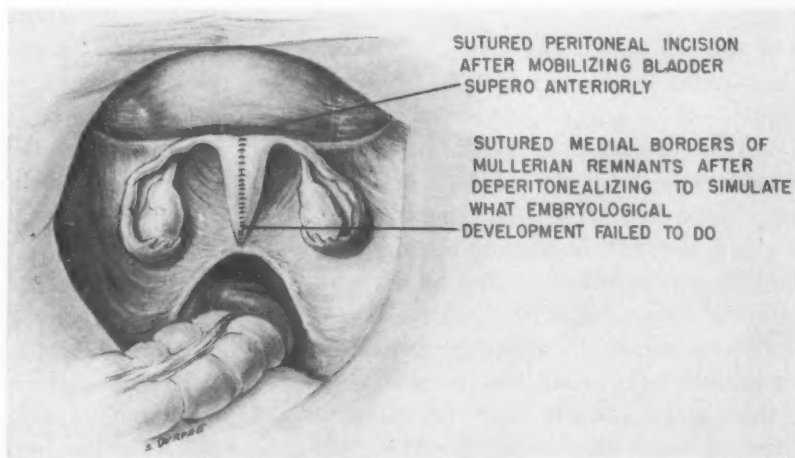


Fig. 3. Suture line after the urinary bladder is mobilized and the Müllerian remnants united.

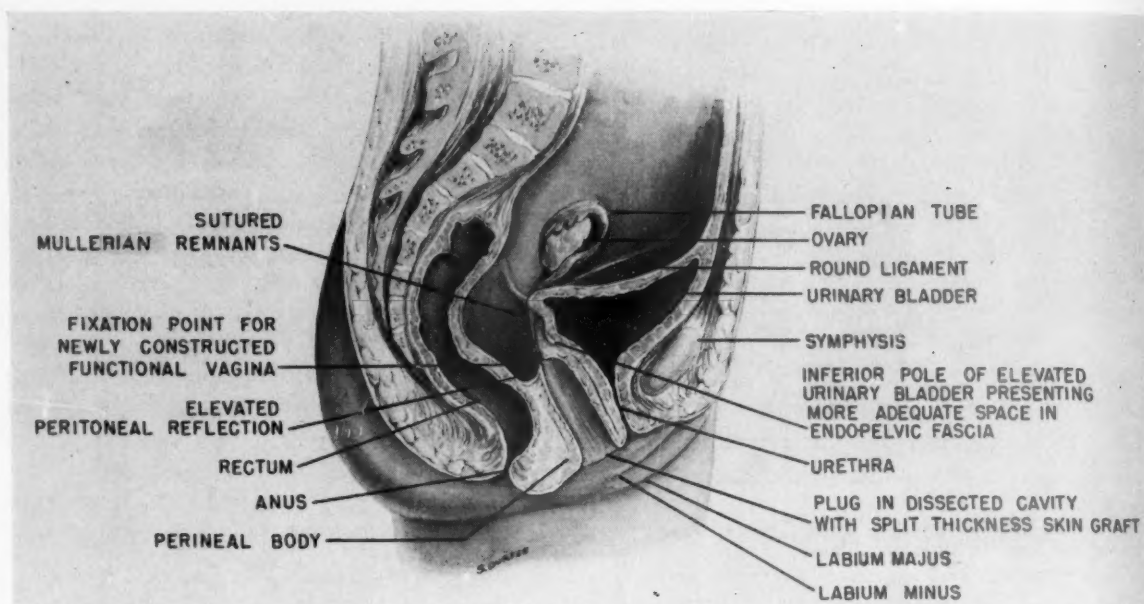


Fig. 4. Note increased space for a dissected vaginal cavity and superior fixation point (illustrated with vaginal plug in place).

tonized, as well as the anterior junction of the uterosacral ligaments. The Müllerian remnants are then sutured together, thus forming a small bridge in a superior plane where they should have been united by nature (Fig. 3). The peritoneal reflection of the urinary bladder is then sutured over this superior aspect of the united Müllerian remnants, thus fixing the bladder in a more anterior position. This gives adequate room for the formation of a vaginal canal at a second stage. The abdomen is closed in the usual manner.

This preliminary procedure establishes a fixation point of support for the future vagina, as well as adequate space.

The *second stage* is performed about 6 weeks after the abdominal operation, through a perineal approach. Split-thickness skin grafts are used to line the vaginal canal according to previously established techniques. Rectal examination before the perineal procedure reveals a high suspension of the remnants of the Müllerian ducts, easily palpable, approximately 6 to 7 cm. above the site in which the vagina is to be made. Labia major and minor are normal and a fossa navicularis is present. A small area of

mucous membrane, of hourglass contour, circumscribes the orifice of the urethra and extends downward to the point where the vagina normally opens externally.

The patient is prepared, draped, and catheterized with a Foley catheter which is left in place. The left thigh is prepared and draped as a donor site for the skin graft. The graft, 0.012 inch thick, 8 inches long, and 3 inches wide, is removed with the dermatome. The skin is placed around a prosthesis form specially prepared with a coating of sulfur-free polyethylene plastic. The skin is wrapped with the outside next to the form; edges are overlapped and smoothed over each other. The skin adheres closely to this form and does not need to be sutured. The skin-covered prosthesis is covered with gauze and kept moist until it is inserted.

After the donor site is dressed, the patient is placed in the lithotomy position. The labia are retracted and sutured laterally for exposure. A half-moon incision is made, partially circumcising the lower half of the small mucous tag situated just beneath the orifice of the urethra and anterosuperior to the medial borders of the fossa navicularis. This incision is then extended for ap-

proximately 2 cm. and deepened slightly until the smooth, white endopelvic fascia is exposed. At this point, digital dissection is carried out in a lateral plane posterior to the bladder and anterior to the rectum, superiorly toward the previously united Müllerian remnants and anterior to the perineal body. The bulbocavernosus is lateral, deep transverse perineal muscles are posterior, and the levator ani are posterior and lateral to this plane of dissection. One finger is placed in the rectum for guidance and dissection is accomplished with a minimum of bleeding. Upon the completion of the dissection superiorly for approximately 7 cm., the area is exposed with retractors. Bleeding points are controlled. A small bulge can be seen at the superior pole where the bladder has been superimposed on the Müllerian remnants by the preliminary procedure. Course of the lateral dissection is guided by the levator ani muscles. After completion of the dissection, a midline episiotomy is done to enlarge the orifice for reception of the prosthesis form with the skin graft in the prepared site, without risk of wrinkling of the graft during the insertion (Fig. 4). The episiotomy site is then sutured snugly to hold the vaginal plug in place. A Foley catheter is left for drainage.

#### Postoperative course

Patients were confined to bed for 7 to 8 days. After 10 days, following removal of the Foley catheter, the vaginal plug was removed, at which time about 90 per cent healing of the skin graft had occurred. Because the first 3 patients had some purulent discharge, the fourth patient was instructed to use Gantrisin vaginal cream, which proved effective in minimizing this troublesome symptom. Patients received instructions for removal and reinsertion of the polyethylene plastic vaginal plug, for the maintenance of dilatation and prevention of primary constriction.

Patients were discharged from the hospital, 19, 12, 22, and 15 days after admission, respectively. All were in satisfactory condition.

#### Results

All the patients expressed satisfaction with the results of the procedure. They are reassured and relieved of much of their emotional anxiety. Examination of the last unmarried patient revealed a vagina that appeared completely normal. In resiliency, "feel," depth, capacity, and physical appearance, it is a normal vagina. The 3 married patients report that they carry on a satisfactory sexual life with normal orgasm and a feeling of pleasure during intercourse.

Subsequent examination of multiple vaginal smears as stained by the Papanicolaou technique does not reveal conclusive evidence that the vaginal transplants are undergoing cyclical changes.

Congenital absence of the vagina is a distinct entity which should not be confused with atresia of the vagina. In the latter, there is partial development of the vagina which remains in a laminary cordlike state. Treatment for such cases has been described<sup>15</sup> but the condition should have been termed "atresia" and not "absence of the vagina."

#### Summary

After a short review of the embryologic development of the Müllerian ducts, a two-stage surgical technique is described which aims to simulate, in the preliminary abdominal phase, the anatomic conditions of normal development. The abdominal procedure establishes a fixation point for support of the new vagina and establishes adequate space for construction of the vagina within the endopelvic fascia. At the second perineal procedure, a new vagina is constructed by means of a skin graft taken from the thigh, according to current techniques.

This operation has been used successfully in 4 young women with congenital absence of the vagina who had normal ovaries and secondary female characteristics. Three of the patients are married and experience satisfactory sexual relations. Relief of emotional disturbances related to the anomaly has been striking in all 4 patients.

In describing the operation for correction



of the absence of the vagina, it is suggested that the term "construction of a functional

vagina" be used to avoid the term "artificial" with its connotation of abnormality.

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# Marsupialization of vulvovaginal (Bartholin) cysts

Report of 140 patients with 152 cysts

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FOUR objections to the excision operation of vulvovaginal (Bartholin) cysts are: (1) the perineum is deprived of an important secretion; (2) the recurrence rate is too high; (3) hemorrhage, hematoma formation, and damage to surrounding structures can be serious complications; and (4) the operation is not feasible when the cyst has ruptured through or under the skin. Despite warnings in many texts, the general tendency is to regard the excision of a vulvovaginal cyst as a routine, minor procedure, and little consideration is given to the limitations, dangers, and poor results that occur so frequently. In 1950, I advanced the simple operation of marsupialization with construction of a new mucocutaneous junction as a means of eliminating these objections.<sup>1</sup> This operation is not difficult and it can be done under almost any conditions, including those peculiar to the terminal months of pregnancy.

## Surgical pathology

The diagnosis of a vulvovaginal cyst usually is obvious although a tumor may imitate a cyst. As the cyst grows or is infected, it becomes uncomfortable, reduces the inclination for coitus, and may interfere with walking and sitting.

How much or what part of the duct is involved in any given case cannot be estimated. All of the duct is not always included and it may be that asymmetrical distention may account for differences in the presentation of the cyst on the labia. When all of the duct is not involved, the remnant may be a source of recurrence even if it has been ligated. This misfortune can-

not be rare because, of the 140 patients, 22 had one or more recurrences. One patient had had 13 previous operations. Ten of these were for drainage and the other 3 were attempts at total excision; but she still had a cyst.

As the distention and infection continue, the wall becomes thick and friable and the surrounding tissues are swollen and edematous. Dissection of a cyst wall under these conditions is almost impossible, and, if the operator persists and enters the corpus cavernosa, hemorrhage from this vascular structure can indeed be severe and hard to control. The wall, difficult enough to identify in this state, then is lost in a flood of blood and may be another source of recurrence.

If the distention and infection are not released, the cyst may rupture beneath or through the skin. In either event, immediate operation is imperative. The former incites a cellulitis that follows the subcutaneous fascia over the abdomen and down the thigh; and, in the latter event, there should be as little delay as possible while the cyst is still large enough to work with and before its wall has retracted.

If an attempt to excise a cyst has failed, then scarring and the loss of anatomical landmarks render succeeding operations much more difficult. The rigidity and density of the structures reduce the diameter to which the cyst can expand before it becomes uncomfortable again. Thus, the problem of disposing of the cyst is compounded by these new factors which increase with each operation regardless of its nature.

The contents of the cysts vary from a



Fig. 1. A typical cyst. The length and position of the incision close to the base of the hymenal ring is shown by the dotted line.

mucoid, opalescent fluid to a dense, malodorous, purulent material. The variety of organisms which were found and the fact that over one fourth of the cysts contained uninfected fluid were indications that infection did not cause the disease but was due to secondary invaders. Four of the cysts were filled with blood clots. The source of the bleeding could not be discovered, but the cysts were treated in the same manner as all the others.

#### Technique of marsupialization

The objectives of marsupialization are to construct a new mucocutaneous junction between the wall of the cyst and the skin of the labia and to place it in approximately the normal position so the secretion will be released on the vulva. The same operation with suitable variations is done regardless of whether the cyst is infected, ruptured, or recurrent.

A curved incision is made through the labial skin about 0.5 cm. laterally and parallel to the base of the hymen along the whole length of that structure (Fig. 1).



Fig. 2. Dissection between the cyst and the skin has been carried far enough to permit the incision into the cyst wall to be almost as long as that in the overlying skin.

It should be deep enough to enter the areolar tissue between the cyst and the skin. Following this line of cleavage, the whole dome of the cyst is exposed (Fig. 2), an incision made into it, and the cyst wall grasped at once before it has a chance to retract. The cyst is then opened completely and the circumference of the incision held with Allis clamps (Fig. 3).

The cyst is then irrigated with warm saline solution (Fig. 4). This step is especially important for it clarifies the cyst wall, particularly of recurrent cysts, and washes away all infected debris. Sometimes one or more constrictions separate the cyst into segments. These constrictions must be divided so that when the cyst resumes the contours of a duct it will be uniform in diameter. The epithelium of the cyst wall is then sutured accurately to the epithelium of the labia. The needle must skip the areolar tissue and pick up only the cyst wall and skin (Fig. 5). Fine catgut on Atraumatic needles is superior to nonabsorbable sutures. The aperture should be as large as it can be made—if possible, large enough to ad-

mit 2 fingers—and, upon release of the clamps, it should disappear under the labia (Fig. 6).

If the cyst has ruptured either through or under the skin, the problem of identifying the cyst wall is encountered. A large incision is necessary for drainage of the surrounding infection, and it should be in the same place as if the cyst were intact. Usually the rent in the cyst wall is small but, if it cannot be found, the collapsed cyst can be located by palpation, and an opening made into it. Then after irrigation and exposure of the cavity, the operation should proceed as if the cyst had not ruptured. Additional measures may be required, depending on the spread of the infection. Suturing in the presence of this infection does no harm and the sutures will hold until the infection subsides.

A recurrent cyst presents different problems. It is better to wait until the cyst has reached its maximum size before operation is undertaken, although severe pain may force intervention while it is still small. The scarring and rigidity of the tissues prevent proper exposure of the dome; hence it usually is necessary to plunge the scalpel di-

rectly into the cyst and at once search for the lining. Since the epithelium of the cyst wall and labia are fixed, mobilization of one or the other is required. Usually the skin can be undermined more easily, and, after irrigation and exploration of the cyst in search of pockets, the suturing must be done with great care to insure apposition of the epithelium. Retraction of the cyst wall is much less a problem than the covering of the circular raw surface between the cyst and the skin. This procedure was carried out in the patient who had had 13 previous operations and the result is shown in Fig. 7. In this case, the skin was drawn into the cyst and held there with sutures.

The majority of patients are ambulant and leave the hospital the day after operation. Postoperative care is done at home. It consists merely of keeping the area clean by immersion twice a day in the bathtub. Dilatations are unnecessary and the aperture will shrink to half its former size within a week. After 4 weeks, it will hardly admit the end of an artery forceps (Fig. 8).

Antibiotics are of no value once the blockade of the duct has begun. Moreover, they are powerless to prevent recurrence, since



Fig. 3. The cavity is irrigated with warm saline to remove debris, mucus, and purulent material and to clarify the cyst wall.



Fig. 4. Bleeders in the skin have been tied and suturing with fine catgut on Atraumatic needles started. Allis clamps hold the cyst wall to the skin but the needle must pick up each layer separately so as to skip the intervening areolar space.





Fig. 5. Suturing has been completed. Tagging of the sutures is not necessary but was done in this case for illustrative purposes.



Fig. 6. The operation has been completed and the aperture is disappearing under the labia. This aperture was completely covered by the labia, thus insuring the release of the secretion of the gland on the vulva.

the return of the disease depends upon factors which have nothing to do with infection. However, antibiotics are useful after the operation to hasten the reduction of the inflammatory reaction and thus shorten the period of disability.

Exception has been taken to the length of the incision,<sup>2,3</sup> the omission of drains, the exposure of the dome, and the use of absorbable sutures.<sup>4</sup> When the cyst is opened, it is easy to see why incision and drainage are inadequate and recurrence after excision is so frequent. The wall retracts immediately and sometimes almost disappears. This retraction is a factor to be reckoned with and is one of the reasons why Davies<sup>5</sup> had difficulty maintaining a stoma even with continuous drainage for several weeks. As the inflammation subsided, the cyst wall withdrew farther and farther from the skin, permitting union across the opening. Mobility of both the cyst wall and skin encourages accurate apposition and allows retraction of the cyst to pull the labial epithelium along with it. The incision into the cyst should traverse its whole diameter, and the skin incision is a trifle longer. Shrinkage is so rapid and complete that, regardless of the length of either incision, only a small meatus remains. Silk or cotton sutures certainly are undesirable in an infected area. Drains may stimulate adhesions between the surfaces of the cyst wall and thus defeat the purpose of the operation.

### Results

This series consists of 140 patients who had 152 cysts. Twelve women had bilateral cysts, but only 4 had both cysts simultaneously. In the other 8, 4 months to 5 years intervened before the appearance of the second cyst. As might be expected, the largest number of cysts occurred during the period of greatest sexual activity. The youngest patient was 16 years of age and the oldest 65. Only 6 were beyond the age of 50. Race and gravidity were of little moment. Twenty-two patients had recurrences from former operations, but, except in a few, there was nothing to indicate the nature of that pro-

cedure. The recurrences from this series are not included.

One hundred and eight cysts contained purulent material; in 40 the fluid was not infected; 4 were filled with blood. Three simple cysts developed during the terminal months of pregnancy. Two were discovered during delivery and operation was done immediately after the placenta was delivered and the episiotomy repaired. The third cyst ruptured under the skin about a week before term. Marsupialization was done as an emergency procedure and did not affect the delivery or convalescence.

There were 4 recurrences. The operators of 3 believed their dissection was inadequate and the apertures were too small. No reason was offered for the fourth recurrence. Bleeding from small arteries in the skin incision happened only once. Since the hemorrhage was on the surface, it was easily controlled and did not form a hematoma.

The results were excellent in all cases, including 3 of the recurrences in which marsupialization was repeated. There were no sequelae of any kind and the apertures were entirely adequate. Infection disappeared rapidly and did not persist in a single instance. Scarring was minimal. In fact, in many patients, after an interval of years, the aperture was almost as difficult to find as the original.

#### Comment

Little is found in the literature to indicate the impairments that frequently follow the conventional excision operation. Today there is an increasing awareness of and concern for the total effect of treatment on the patient rather than consideration of the surgical result alone. The possible psychological effects of operation and particularly operation upon the genitals should be of importance equal to that of the pathologic, endocrinologic, or surgical aspects of an illness.

The loss of one vulvovaginal gland may be of no consequence to the majority of patients, but there are instances where just the absence of one half the lubricating fluid



Fig. 7. This patient had had 13 operations in 3 years. Three were attempts at excision and the remaining 10 were incision and drainage. Marsupialization was accomplished by mobilizing the skin and attaching it with fine sutures to the lining of the cyst which, at the time, was comparatively small and tightly distended with purulent fluid. This photograph was made 8 years after operation.



Fig. 8. The completed operation 2 months later. The aperture is in the center between and medial to the fingers. Note that the retraction of the cyst wall has pulled the labial mucous membrane into the duct. This aperture, which was so large when the operation was completed now will admit only the end of an artery forceps.

has precipitated dissension and discord. How often tender, irritating scars follow excision is not known, but Novak<sup>6</sup> has commented that they can be quite annoying in this sensitive region.

Bilateral cysts were removed at different times from each of 2 patients. The loss of one gland was not noticed, but the absence of secretion during coitus after the second was excised compelled these women to resort to artificial lubricants which were neither aesthetic nor satisfactory. In addition, the quantity of mucus descending from the vagina was inadequate, and dryness and itching of the vulva was extremely aggravating.

There are no statistics regarding the rate of recurrence, the incidence of hemorrhage, or the number of lesser sequelae arising from the excision of vulvovaginal cysts. This series of cases demonstrates that marsupialization offers a simple and reliable means for curing this lesion without any of these risks. It has the additional advantages of restoring the normal function of the gland, reducing the period of disability, and shortening the hospital stay to half the customary time.

### Summary

The excision operation for curing a vulvovaginal cyst is not without danger, complications, or sequelae. Some of these, including the potential loss of the second gland, can have serious physiologic and psychological implications.

Marsupialization of the cyst eliminates all the objections to the excision operation. It consists of making another meatus for the duct by creating a new mucocutaneous junction. The cyst then collapses and resumes the contours of the duct, and this new aperture provides an adequate outlet for the secretion of the gland. This operation can be done without risk under almost any conditions.

A series of 140 patients who had 152 cysts, with 4 recurrences, is presented. An excellent result was obtained in all cases but one, which could not be followed. There were no complications or sequelae. Further advantages were reductions of the periods of disability and hospitalization.

I wish to express my appreciation to the members of the surgical staff of the Petersburg General Hospital for permission to include their cases in this series.

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# Basement membranes in the female genital tract

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IN MANY descriptions of invasive cancer of the vulva, cervix, and even endometrium, the phrase "penetration through the basement membrane" is used. We, personally, have been struck by the variability in the density, continuity, and even the frequent absence of a membrane between epithelium and stroma in most structures in the female genital tract. We have, therefore, undertaken this study on the morphology of the basement membrane in the female generative tract and have reviewed the recent literature on its composition. After completion of the first few drafts of this manuscript an article by Dougherty and Low<sup>2</sup> appeared entitled "The Fine Structure of the Basement Membrane of the Uterine Cervical Epithelia." These authors considered that a basement membrane was present between the stratified squamous epithelium and the underlying stroma of the cervix and that a similar membrane existed under the endocervical columnar epithelium. These membranes were submicroscopic and  $0.03\ \mu$  thick. They could be demonstrated only by electron micrography. It is obvious that such a membrane is not the same as the true "base-

ment membrane" which is easily demonstrable by light microscopy.

## Basement membrane

The term *basement membrane* refers to a specialized layer of intercellular substance between the underlying connective tissue and many epithelial and endothelial surfaces.<sup>5</sup> The exact composition of the structure has long been debated. First considered to be merely a condensed layer of reticular fibers, it has more recently been shown to contain a variable amount of amorphous ground substance. The condensed ground substance, usually seen only with special stain techniques, is considered to be the basic material of the basement membrane.<sup>5</sup> At present the consensus is that the basement membrane is composed of an optically homogeneous condensed layer of amorphous ground substance in which there may be interspersed a variable number of reticular fibers.<sup>5, 13</sup> We believe that a true basement membrane must have two definite margins or borders. Certainly it appears to have such sharp borders in the kidney and around sweat glands.

The function of the basement membrane is generally considered to be that of support and foundation for the cells that overlie it. However, a second function, that of transport by diffusion of nutrients and wastes to and from the cells, is equally important.<sup>7</sup> Some cells have short processes that penetrate the membrane, perhaps to attach them more securely or to increase the area

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for diffusion.<sup>12</sup> Incidentally, the basement membrane is not demonstrable in several critical areas where strength is obviously required.

### Ground substance

The ground substance is an optically homogeneous, amorphous continuum forming part of the intercellular substance in which cells and fibers are suspended.<sup>5</sup> It has a high content of mucopolysaccharides and glycoproteins (which are mucopolysaccharide-protein complexes). These mucopolysaccharides are high molecular weight compounds composed of repeating units, each made up of equimolar parts of an amino sugar (glucosamine or galactosamine) linked with one of the two isomeric forms of glucuronic acid.<sup>1, 14</sup> In some cases a sulfate radical is present in the repeating unit. Hyaluronic acid (a nonsulfated mucopolysaccharide) was the first of these discovered, and is now known to be present in the ground substance of all tissues.<sup>1</sup> The glycoprotein complexes are believed to be organized on a submicroscopic or molecular level by a process of polymerization.<sup>5</sup> Gersh and Catchpole<sup>5</sup> have hypothesized that the degree of polymerization of the ground substance is the greatest in the basement membrane which is, therefore, highly condensed and insoluble.

The use of recently developed histochemical modifications of the Schiff reaction, an old established test for aldehydes, has opened up new possibilities in the study of mucinlike substances of the connective tissue, including the mucopolysaccharides of the basement membrane. Almost simultaneously three investigators, Hotchkiss,<sup>8</sup> McManus,<sup>11</sup> and Lillie,<sup>9</sup> discovered that periodic acid, a strong oxidizing agent, could be used on tissue sections to liberate aldehydes from polysaccharides in such a fashion that the sites of aldehyde liberation could then be stained by means of the Schiff reaction. The Schiff reagent is a basic fuchsin which has been bleached with sulfurous acid. Aldehydes restore to the bleached dye the color of the unbleached

basic fuchsin. The whole procedure, including the preliminary treatment of sections with periodic acid and the subsequent exposure of the section to the Schiff reagent, is commonly referred to as the PAS technique.<sup>7</sup>

It was soon learned that the PAS technique was remarkably effective in demonstrating basement membranes.<sup>1, 11</sup> There has been much discussion, however, about the particular component of the basement membrane which stains so brilliantly with this technique.<sup>5</sup> Lillie developed an allochrome procedure by which the basement membrane retains the purple color imparted by the PAS technique, but with which the reticular fibers are colored blue.<sup>10</sup> Thus it is the condensed ground substance and not the reticular fibers per se which is responsible for the reactivity of the basement membrane.

### Fibers

The formed elements which compose the other important part of the intercellular connective tissue are the reticular, the collagenous, and the elastic fibers.<sup>7</sup> The last are contractile fibers with specific staining reactions and well-known distribution. They are not related to the basement membrane, are relatively sparse in the tissues of interest to the gynecologist, and will not be discussed here.

Collagen fibers are coarse nonbranching birefringent bundles of fibrils which stain differentially with trichrome stain, take a light brown stain with silver techniques, and stain palely with PAS. Treatment with alkali will dissolve the interfibrillar cement substance and allow demonstration of even smaller fibrils.<sup>1, 7, 15</sup>

Reticular fibers are fine branching non-birefringent fibers which stain differentially with certain silver impregnation methods with a deep black color. In some instances the fibers themselves appear to take a PAS stain whereas under different circumstances they do not. Under the electron microscope the reticular fibers are seen to form a felt-work between the wider collagenous fibers, an arrangement which has been compared

to chicken wire on fence posts. The individual fibers are 0.01 to 0.05  $\mu$  in diameter and do not form bundles of fibers. It is known from electron microscopy and x-ray diffraction studies that the reticular fibers display the same axial periodicity as the collagenous fibers (0.065  $\mu$ ),<sup>6, 15</sup> and at present the molecular structure of the reticular fiber is considered to be similar to that of the collagenous fibril.<sup>1, 15</sup>

Even before the similarities of microstructure and chemical composition were known, it was considered that there was a close relationship between the collagenous and reticular fibers. It has been noted even with the ordinary microscope that reticular fibers are often seen to merge with collagenous fibers as brooks and streams join to form a river.<sup>1, 15</sup> The difference in silver staining reaction of the two types of fibers had been attributed to variation in the amount of area per fiber available for absorption of the silver salts, and the reticular fibers were considered to be nothing more than young collagenous fibers.<sup>13</sup> It is known that the reticular fibers are found in certain embryonic tissues much earlier than the collagenous fibers and that in some tissues at least the proportion of collagenous fibers increases with the age of the animal.<sup>1, 3, 4, 6, 13</sup>

There are two basic processes for the selective demonstration of collagen and reticular fibers; silver impregnation from alkaline solution and staining with acid aniline dyes from strongly acid solution.

The silver methods, though somewhat uncertain in their action, serve well to differentiate between reticular and collagenous fibers. The former are colored black and the latter, brown, lavender, and gray in varying shades and tones.

The method commonly used in the demonstration of collagen is the trichrome stain; the selective collagen staining with acid dyes apparently depends on the selectivity of collagen for certain acid dyestuffs from fairly strongly acid solutions. We did not find it necessary in this work on basement membranes to use trichrome stains routinely, although several were studied incidentally.

### General method

Representative sections of vulva, vagina, cervix, endometrium, oviduct, ovary, and other miscellaneous tissues along with control sections of trachea and kidney tissues were selected. The numbers in each group will be enumerated later. These sections were stained with hematoxylin and eosin and the PAS stain.<sup>11</sup> Many, but not all, were stained with Wilder's reticulum and Lillie's allochrome method.<sup>10</sup> Sections were then studied for the presence of a "basement membrane" and where present these were measured with a micrometer ocular.

### Findings

**Controls.** Sections of kidney (Fig. 1) and of trachea were used as controls. In the kidney a thick homogeneously stained structure with sharp borders was particularly evident under the epithelium of Bowman's capsule of the glomerulus. The membrane was continued under the glomerular epithelium and around the various tubules. In the trachea a basement membrane under the epithelium was comparable in sharpness to that found in Bowman's capsule.

In most structures there was a condensation of reticular fibers in the areas where a basement membrane was present. In Bowman's capsule in the reticulum preparations counterstained with hematoxylin and eosin, the basement membrane stained per se with reticular fibers present only in the peripheral portions of the membrane. In spite of the definite basement membrane there was a paucity and in many areas an absence of reticular fibers in the glomerulus proper.

In the trachea the condensation of reticular fibers was quite heavy but did not form as thick a layer as the substance stained with PAS.

**The vulva.** Six specimens from patients varying in age from 18 to 68 were studied. With the PAS stain the width and continuity of a subepithelial membrane was very variable (Fig. 2). No demonstrable membrane was present in two and in all except one specimen it was discontinuous.

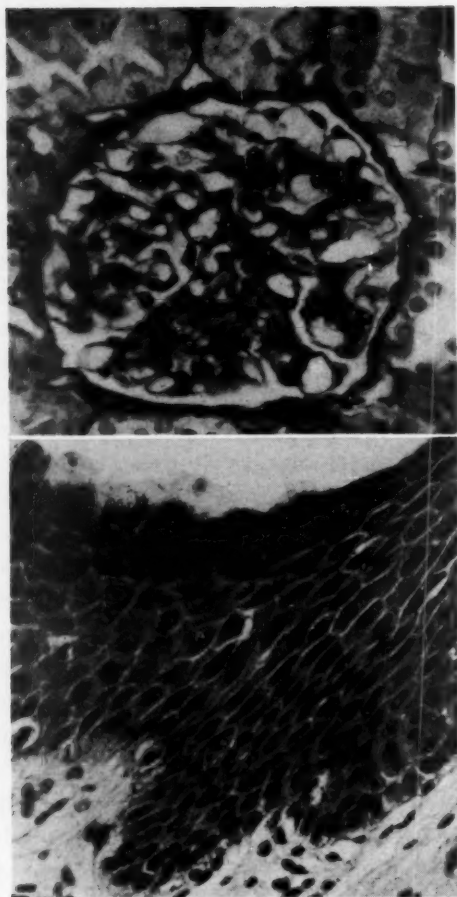


Fig. 1. This slide of normal kidney and all other slides photographed are stained with the PAS technique. Note the heavy basement membrane under the epithelium of Bowman's capsule of the glomerulus. There is a lighter basement membrane around the tubules. ( $\times 400$ ; reduced  $\frac{1}{3}$ .)

Fig. 2. No basement membrane is present under the squamous epithelium of the vulva. ( $\times 362$ ; reduced  $\frac{1}{3}$ .)

In none of these tissues was the condensed PAS-positive material a sharp bordered structure of uniform width or staining properties. There was a continuous moderately thick layer of reticular fibers underlying the squamous epithelium in all but one specimen.

A continuous basement membrane 2.3 to 3.8  $\mu$  in width with sharp margins and intense PAS-staining properties surrounded the sweat glands of the vulva (Fig. 3). Actually the contrast between this membrane and the lack thereof under the squamous epithelium was one of the precipitating factors in initiating this study.

**The cervix.** The squamous epithelium of

the ectocervix was studied with the PAS technique in 6 specimens. A stainable membrane was absent in one specimen; of the remaining 5, 3 showed a discontinuous membrane of variable thickness (Fig. 4), and only 2 showed a continuous membrane. As in the vulva, the stromal margin was not sharp and the intensity of staining was variable.

Five of the slides were also stained for reticular fibers. In 4 there was an irregular and discontinuous condensation of reticular fibers of moderate thickness underlying the squamous epithelium; in one no such condensation was found.

For the study of the endocervical glandular epithelium 2 additional specimens stained with PAS technique were available. On the 8, none had a continuous membrane (Fig. 5); 5 had a slight condensation of ground substance; 3 lacked any condensation.

Six slides of endocervix were stained for reticular fibers. Three of 6 showed a continuous, moderately thick condensation of reticular fibers underlying the epithelium; the other 3 showed a discontinuous layer of variable thickness.

**Endometrium.** Of the 13 specimens of endometrium studied, 4 were proliferative, 5 secretory, 2 menstrual, and 2 were from senile uteri. No consistent differences in the character of a subepithelial membrane could be determined on the basis of this small number, nor was any consistent difference noted between the basal and the superficial glands.

A thin and discontinuous layer of condensed ground substance was present in 9 of the 13 specimens, absent in 2, and fairly thick in the other 2. These latter were from senile uteri. In one of these, however, it was inconstant, being absent around most of the superficial and some of the basal glands.

Eight of the specimens were stained for reticular fibers. A thin layer of condensed fibers was present in all 8 but was discontinuous in 6.

**Endosalpinx.** Twenty specimens of endosalpingeal epithelium stained with the PAS



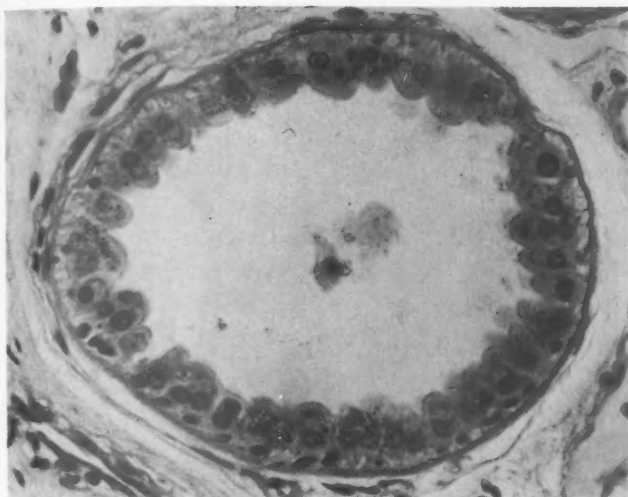


Fig. 3. An apocrine sweat gland of the vulva. Note the fairly heavy basement membrane underlying the epithelium. ( $\times 400$ ; reduced  $\frac{1}{3}$ .)

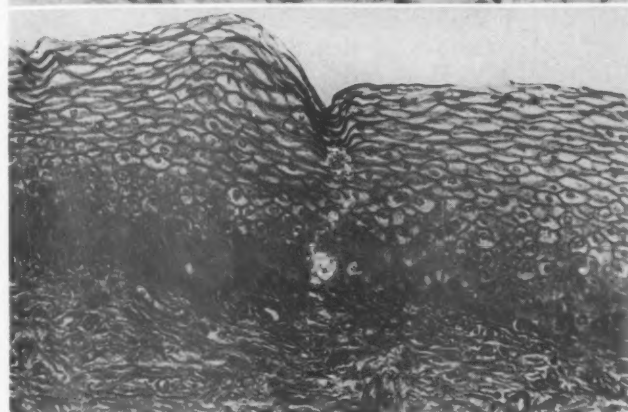


Fig. 4. There is no basement membrane underlying the stratified squamous epithelium of the ectocervix. ( $\times 250$ ; reduced  $\frac{1}{3}$ .)

technique were available for study. Sixteen were from women of functional age and 4 from postmenopausal women. The findings were quite variable. In 7 of the 20 no condensation of PAS-positive material was present; in 10 a discontinuous and variably thick membrane was noted; in 3 a fairly thick continuous membrane was present. In 2 of the latter 3, the specimen was limited to the tubal fimbria.

Of the 7 sections also stained for reticular fibers, the condensation of fibers was slight and discontinuous in 5 and of moderate thickness and continuous in the other 2 (one functional and one senile).

**Mesophrenic structures.** All 7 of the specimens of mesonephric tubules and ducts (Fig. 6) of the broad ligament stained with PAS technique showed a sharp bordered continuous basement membrane of 2.0 to 3.0  $\mu$  in thickness. Two of these were also

stained for reticular fibers and showed a condensation of reticular fibers of corresponding thickness.

**Rete ovarii.** This little-studied structure is composed of interweaving clefts, tubules, and cords. The epithelium varied in different areas and the findings in the 11 specimens stained with the PAS technique correlated with the variation in epithelium.

In the central portions of the rete, particularly when clefts and cords are present, the epithelium is low and there is no underlying PAS-positive layer. In the more peripheral portions the epithelium is higher, even columnar, and has a continuous, sharply defined, homogeneously stained basement membrane of 1.0 to 3.0  $\mu$  in thickness (Fig. 7). It is believed that these latter tubules are homologues of the tubuli recti of the testes and do have a basement membrane while the lower rete epithelium does not.



Three specimens were also stained for reticular fibers. In one the layer of reticular fibers adjacent to the epithelium was continuous and moderately thick; in the second it was discontinuous; in the third it was absent.

**Germinal epithelium of the ovary.** A true basement membrane 1.5 to 2.5  $\mu$  in thickness was found under the germinal epithelium of the ovary (Fig. 8). Eleven specimens were available stained with PAS and 7 of these also had reticulum stains. With the PAS, Lillie allochrome, and modified allochrome, the basement membrane was definite and obvious with sharp borders,

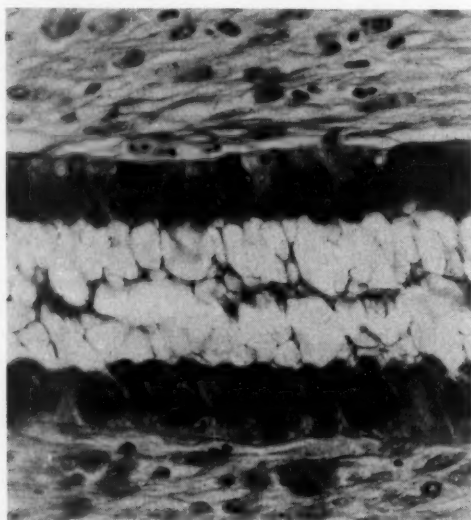


Fig. 5. This section includes portions of an endocervical gland. There is no basement membrane underlying the epithelium. ( $\times 400$ ; reduced  $\frac{1}{3}$ .)

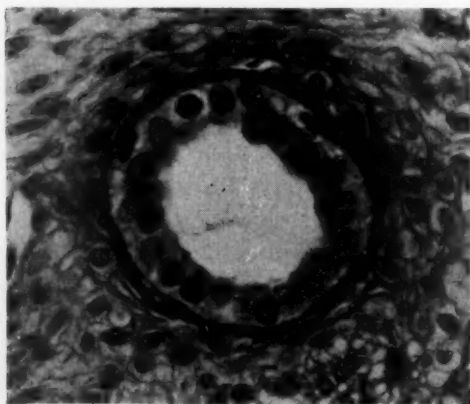


Fig. 6. A cross-section of the mesonephric duct remnant normally found in the broad ligament. Note the heavy basement membrane. ( $\times 625$ ; reduced  $\frac{1}{3}$ .)

and was homogeneously and brilliantly staining. A condensation of reticular fibers of variable degree (and not correlating with the thickness of the PAS-positive material) was present in all.

There was no basement membrane under peritoneal mesothelium. The contrast between the membrane under the germinal epithelium and its lack under immediately adjacent peritoneal mesothelium of adhesions to the ovary was striking (Fig. 8). Two specimens had luckily been fixed immediately so that the peritoneal mesothelial germinal epithelial junction was not desiccated or stripped off. Here again the contrast and abrupt transition was striking.

**Incidental observation.** A basement membrane separates the granulosa from the theca in the very early follicle. It apparently develops after the first layer of granulosa cells change from flattened to typical cuboidal cells. It disappears during later maturing of the follicle. Our observations are inadequate to discuss this further at this time.

#### Comments

It is obvious that we believe that no true basement membrane is present under the skin of the vulva, under the stratified squamous epithelium and columnar epithelium of the cervix, in the endometrium, or in the tube. The use of "penetration of the basement membrane" by carcinomas in such areas is, therefore, very loose and should be abandoned.

Note was made of the claims of Dougherty and Low<sup>2</sup> of a submicroscopic basement membrane 0.03  $\mu$  thick in the cervix. This is in contrast to the 1.0 to 3.8  $\mu$  thickness of a true membrane around sweat glands, under the germinal epithelium of the ovary, in the kidney, and so on. One wonders if their membrane merely represents a space between 2 cell membranes of adjacent cells.

#### Summary and conclusions

1. The term "basement membrane" refers to a specialized layer of condensed ground substance between epithelial or en-



Fig. 7. A section from the hilum of an ovary. Note the heavy basement membrane surrounding most of this portion of the rete ovarii. The arrow points to an area where the rete forms a cord. In this area there is no basement membrane. ( $\times 400$ ; reduced  $\frac{1}{3}$ .)

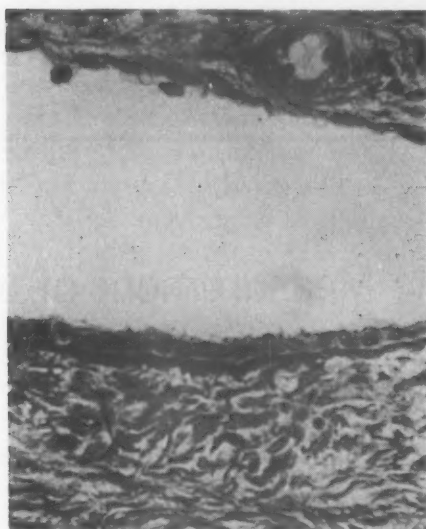


Fig. 8. Ovarian cortex below and an adhesion above. Note that there is a basement membrane under the germinal epithelium of the ovary but none under the peritoneal mesothelium of the adhesion. ( $\times 400$ ; reduced  $\frac{1}{3}$ .)

dothelial surfaces and the underlying stroma.

2. The ground substance, because of its polysaccharide content, is stained with the PAS technique. Reticular fibers may be differentiated from the related collagenous fibers by the silver impregnation techniques, such as Wilder's.

3. Specimens of normal female pelvic organs were stained by these techniques to demonstrate the presence or absence of a basement membrane.

4. The condensation of ground substance and of reticular fibers underlying the following structures: squamous epithelium of vulva and cervix; glandular epithelium of endocervix, endometrium, endosalpinx; and peritoneal mesothelium, was often absent, thin, or discontinuous.

5. Underlying the following epithelia: sweat glands of the vulva; mesonephric tubules of the broad ligament; the columnar portion of the rete ovarii; and the germinal epithelium of the ovary, is a continuous prominent basement membrane with sharp margins.

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## OBSTETRICS

### Measurement of uterine blood flow and uterine metabolism

#### VIII. Uterine and fetal blood flow and oxygen consumption in early human pregnancy

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THE growth of the fetus in utero and its ultimate success at birth depend on a steady supply of oxygen and other nutritive materials from the mother. This supply is secured through continuous adjustments in the circulation in the pregnant uterus and probably in the fetus as well. These adjustments have been somewhat difficult to assess. Animal investigations have dealt mainly with the circulation and metabolism of the fetus in utero and in neonatal

life, with little attention directed to the pregnant uterus itself. The studies in humans have been limited largely to the descriptive aspect of the fetal circulation or to the determination of oxygen saturation in the umbilical vessels during or shortly after delivery.

A few attempts have been made to elucidate the circulatory problems of early human pregnancy. Lind and Wegelius<sup>1</sup> performed angiocardiology in fetuses of 18 to 22 weeks of gestational age and described accurately the trajectories of venous and arterial circulation. The studies of Ramsey,<sup>2, 3</sup> Boyd,<sup>4</sup> and Borell<sup>5</sup> have contributed a great deal to our understanding of the anatomy of the uteroplacental circulation but have provided no quantitative information regarding circulatory dynamics of the fetus and of the pregnant uterus.

The present studies were aimed at (1) measuring the uterine blood flow and uter-

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ine oxygen consumption in early human pregnancy; (2) correlating the changes which occur in uterine blood flow and oxygen consumption with those which occur in the fetus in the same patient and during the same period of gestation; (3) comparing in the same patient two currently used methods for measuring regional blood flow; and (4) obtaining information regarding the adjustment of the fetus to the so-called hypoxic state in utero.

### Material and methods

The studies were carried out on 32 pregnant patients undergoing therapeutic abortion by hysterotomy between 9 and 28 weeks of gestation. Of this number, 20 patients were deleted because the studies were complicated by excessive blood loss during the dissection of the uterine vessels or by difficulties in obtaining blood samples anaerobically from the uterine and umbilical vessels. In the remaining 12 patients, data on the uterine blood flow and oxygen consumption and, to some extent, data obtained on the fetus were considered fairly adequate. The age of the patients varied between 25 and 42 years. None of these patients had a history of organic illness, and the indications for therapeutic abortion were mainly social or psychiatric. Uterine blood flow was measured in the same patient with the nitrous oxide ( $N_2O$ ) technique and with a miniature electromagnetic flowmeter. Details of these two methods have been published elsewhere.<sup>6, 7</sup> Umbilical blood flow was measured with an electromagnetic flowmeter similar to that used in the mother. The procedure was carried out in the operating room under intravenous barbiturate or spinal anesthesia. The abdomen was entered through a suprapubic midline incision and either the right or the left uterine artery was exposed near the point at which it crosses the ureter and was dissected free from the surrounding tissues for a distance of 2 to 3 cm. This segment was then slipped into the channel of the electromagnetic flowmeter which was positioned so as not to produce any

kinking or alteration in the course of the vessel. A polyethylene catheter was inserted into one of the main uterine venous trunks and a similar catheter or a Courmand needle was inserted into the brachial artery. Samples of uterine venous blood and of arterial blood were obtained anaerobically for controls. Thereafter, 15 per cent concentration of  $N_2O$  was administered to the patient through an anesthesia mask and simultaneous arterial and venous blood samples were obtained at appropriate intervals. Electromagnetic recording of uterine blood flow was made before and at frequent intervals during and after the  $N_2O$  procedure.

After the uterine blood flow had been recorded for a period of 20 to 30 minutes, the uterus was opened and a loop of the umbilical cord was delivered through the incision. A segment of the umbilical vein was rapidly freed from the umbilical arteries and slipped into the channel of the electromagnetic flowmeter. The umbilical cord and the flowmeter were then reinserted into the uterine cavity and the recording of the umbilical vein flow begun.\* After the umbilical flow was recorded for 10 to 15 minutes, the cord was again removed and anaerobic samples of blood were obtained from the umbilical vein and from an umbilical artery. When this procedure was completed, the fetus was delivered and its weight and height were recorded.

Blood samples were analyzed for their content of  $O_2$  and  $N_2O$  by methods previously described.<sup>8</sup> Oxygen saturation and capacity were analyzed by a photoelectric method with use of Brinkman's hemoreflexor as described by Zijlstra.<sup>9</sup> In several samples, the results obtained with this method were checked against those obtained with the Van Slyke method, and the difference did not exceed 2 per cent. Average total uterine and umbilical blood flows were obtained by planimetry of the electromag-

\*In several instances, a spasm of the umbilical vessels occurred which disturbed seriously the flow recording. Various procedures were used to relieve the spasm but the most successful one was that of immersing the flowmeter containing the vessel in amniotic fluid in the uterine cavity and waiting until the flow signal became clear.



Table I. Data on blood flow and oxygen consumption of the pregnant uterus from the tenth to the

Pa- tient	Age	Length of ges- tation (weeks)	Total uterine weight (grams)	Uterine O <sub>2</sub> saturation (%)		Uterine O <sub>2</sub> capacity (ml./100 ml.)	Uterine blood flow (EMF) (ml./min.)
				Arterial	Venous		
1	37	10	—	92	86	15.5	51.7
2	29	12	593	90	85	14.1	56.7
3	35	14	636	91	86	16.5	62.2
4	28	14	—	82	75	21.7	—
5	38	15	730	92	86	15.3	66.0
6	42	16	920	90	83	16.0	75.6
7	27	16	—	94	87	15.4	73.6
8	27	16	—	96	88	16.0	72.8
9	38	17	1,020	94	84	14.0	90.5
10	35	19	—	92	84	16.7	98.0
11	25	24	—	90	82	15.0	153.0
12	26	28	—	95	88	17.0	185.0

\*Arterial and uterine venous blood saturation of oxygen and oxygen capacity are also listed. Uterine blood flow and uterine

netic flow complex which had been recorded on a Sanborn dynograph. Uterine blood flow was also calculated from the N<sub>2</sub>O curves and expressed as milliliters per 100 grams of total pregnant uterus as outlined previously.<sup>6</sup> Oxygen consumption of the uterus and of the fetus was calculated from the formula: O<sub>2</sub> consumption = F(A-V), where F = uterine or umbilical blood flow, A = arterial O<sub>2</sub> content, and V = venous O<sub>2</sub> content.

In 5 patients, hysterectomy was performed after the above-described studies had been completed. The uterus and its contents were weighed and the values obtained with the electromagnetic flowmeter computed on the basis of milliliters per 100 grams of pregnant uterus and compared to the values obtained with the N<sub>2</sub>O technique.

## Results

**I. The pregnant uterus.** Table I and Figs. 1 to 4 present the results of the studies on the pregnant uterus between 10 and 28 weeks of gestation.

Uterine blood flow was expressed in 3 different ways, as follows:

A. Total uterine blood flow as computed from the recording obtained with the electromagnetic flowmeter (Table I, EMF, Column 7, and Fig. 1). As was mentioned

above, the transducer unit was placed on one uterine artery only; however, the figures listed in Table I represent the flow to the whole uterus. This calculation was made with the assumption that the same amount of blood flows through each of the two uterine arteries. Although this assumption might not be entirely correct, the error should be small since the values obtained during a given period of gestation were closely similar regardless of whether the right or left artery was used. With this assumption in mind, it can be seen that total uterine blood flow measured by the electromagnetic method increased from 51.7 ml. per minute at 10 weeks to 185 ml. per minute at 28 weeks of gestation (Table I and Fig. 1).

Total uterine blood flow in human pregnancy at term has been roughly estimated from experiments in which the N<sub>2</sub>O and the Na<sub>24</sub> techniques were used.<sup>10-12</sup> The average values have varied from 500 to 700 ml. per minute, with a large individual variation in each series of experiments. Since no data are available for early pregnancy, any tentative comparison between our figures and those reported for term pregnancy can be made only by extrapolation. This procedure, however, will involve a gross error since it does not take into consideration various interfering factors such as different

twenty-eighth week of gestation.\*

Uterine blood flow (EMF) (ml./100 grams/min.)	Uterine blood flow (N <sub>2</sub> O) (ml./100 grams/min.)	Uterine O <sub>2</sub> consumption (EMF) (ml./min.)	Uterine O <sub>2</sub> consumption (EMF) (ml./100 grams/min.)	Uterine O <sub>2</sub> consumption (N <sub>2</sub> O) (ml./100 grams/min.)
—	9.2	4.8	—	0.86
51.7	9.6	4.0	0.67	0.72
56.7	9.8	5.1	0.80	0.54
62.2	—	8.7	—	1.32
—	9.0	9.5	.83	.87
66.0	8.2	9.0	.92	1.08
75.6	—	7.2	—	0.78
73.6	—	7.0	—	0.90
72.8	9.8	10.4	1.24	1.45
90.5	—	8.5	—	1.14
98.0	—	9.0	—	1.08
153.0	—	12.0	—	1.43
185.0	—	22.0	—	—

oxygen consumption have been expressed in three different ways. (For full explanation, see text.)

methods of measuring flow, totally different series of patients, and the changes in blood flow which might be associated with placental aging.

B. Uterine blood flow was calculated from the N<sub>2</sub>O curves and was expressed as milliliters per 100 grams per minute. Computed by this method, the flow varied between 6.6 ml. per 100 grams per minute and 12 ml. per 100 grams per minute with an average of 8.9 ml. (Table I, Column 9, and Fig. 2). The variation in the flow values, however, did not present any relationship to the duration of gestation or to the growth of the uterus and fetus. Two previously reported series<sup>10, 11</sup> on uterine blood flow in human pregnancy at term with the N<sub>2</sub>O method had average values of 12.4 and 15 ml. per 100 grams per minute. Although these averages were higher than those reported here, the individual variation in the two series was equally large, despite the fact that the patients studied in the latter series were all close to the fortieth week of gestation (Fig. 2). Under these circumstances, it appears that the variation in the different values obtained with the N<sub>2</sub>O technique is probably due to the method itself rather than to the changes in the size of the uterus.

Since measurement of uterine blood flow by the N<sub>2</sub>O method gives results which are

expressed on the basis of unit weight of the organ rather than as total flow, the data obtained at term may be compared to those of early pregnancy. From this comparison, it appears that the blood flow per 100 grams of pregnant uterus does not change significantly throughout pregnancy (Fig. 2).

C. In the 5 patients who had undergone hysterectomy, it was possible to calculate the flow obtained with the electromagnetic flowmeter on the basis of milliliters per 100 grams per minute and thus compare this method with that of N<sub>2</sub>O. The values computed in this way were also fairly constant, irrespective of the period of gestation, and they varied between 8.2 ml. per minute and 9.8 ml. per minute. (Table I, Column 8). Although the results obtained with the electromagnetic method varied less than those obtained with the N<sub>2</sub>O method, the flow values of the two methods were closely comparable. Thus, regardless of the method employed, uterine blood flow per unit weight remained fairly constant throughout the course of gestation.

Uterine oxygen saturation ranged from 90 to 96 per cent arterial and from 82 to 88 per cent venous, giving an arteriovenous difference of 7 (Table I). Only one patient (No. 4) had an arterial saturation of 82 per cent and venous saturation of 75 per

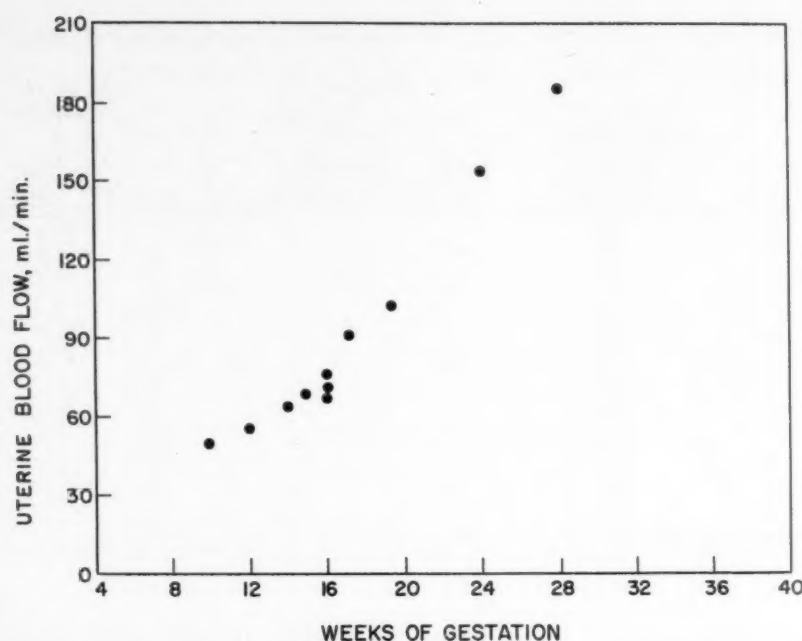


Fig. 1. Total uterine blood flow as measured with the electromagnetic flowmeter placed around the uterine artery. Note the progressive increase throughout the course of gestation. Note also that after the sixteenth week the flow increased at a much faster rate than in the earlier period of pregnancy.

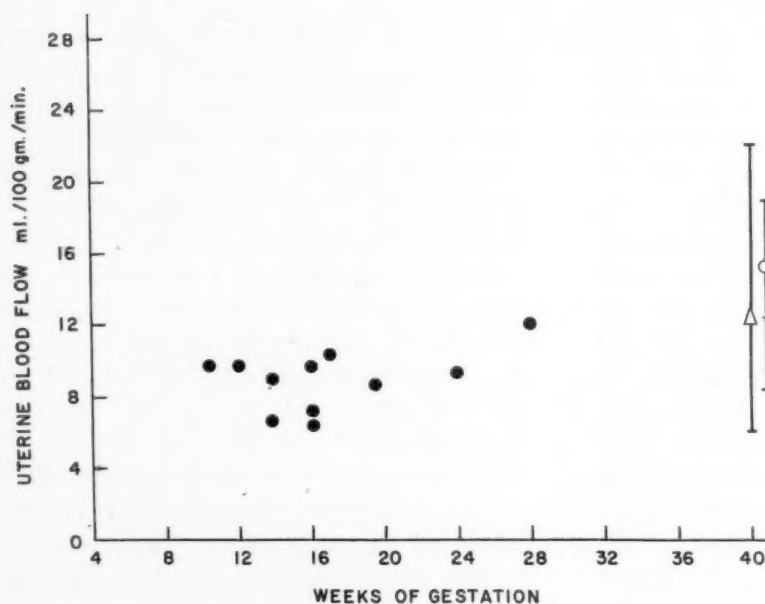


Fig. 2. Uterine blood flow calculated from the nitrous oxide curves and expressed as milliliters per 100 grams of pregnant uterus per minute. In order to facilitate comparison, the figure shows the average and range of values obtained with the same method at 40 weeks by Metcalfe and associates (triangle) and by Assali and co-workers (open circle). Note the wide variation in the flow values obtained with this method throughout the course of gestation. The flow values at 40 weeks were not significantly different from those of early pregnancy, however. Therefore, the blood flow per unit weight of pregnant uterus remains fairly constant throughout the course of gestation.

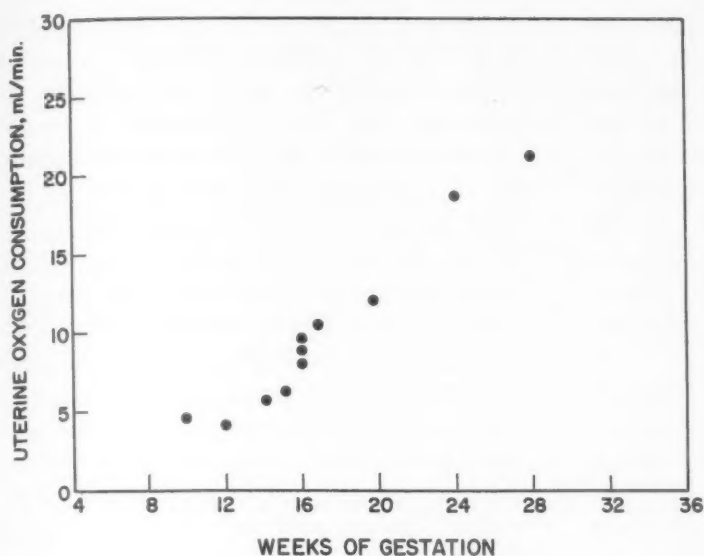


Fig. 3. Total uterine oxygen consumption computed from the electromagnetic uterine blood flow and the arteriovenous difference of  $O_2$  as described under "Material and methods." Note the progressive increase in oxygen consumption, particularly the striking rise after the sixteenth week of gestation.

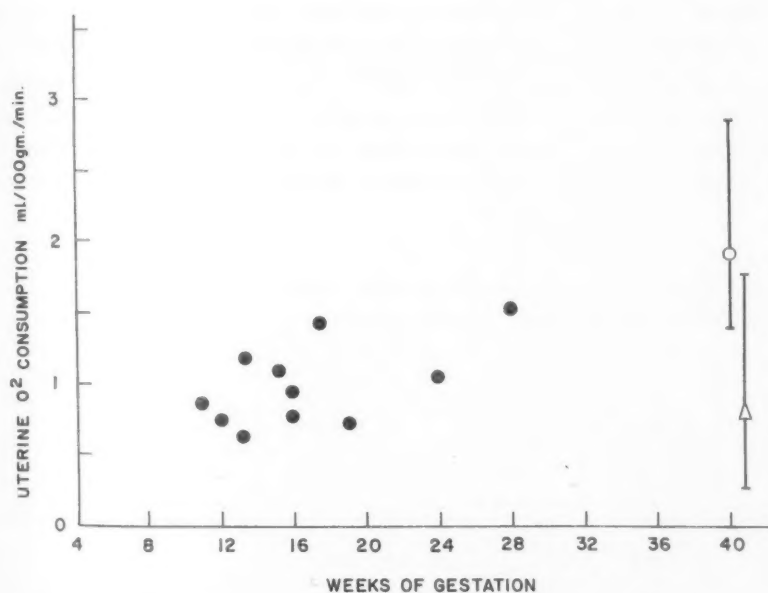


Fig. 4. Uterine oxygen consumption calculated from the  $N_2O$  flow values and the arteriovenous difference of  $O_2$  and expressed as milliliters per 100 grams per minute. In this figure, also, are listed the values obtained at term by Metcalfe and associates (triangle) and by Assali and co-workers (open circle). Note that the variation in the values of oxygen consumption throughout pregnancy was similar to that of blood flow listed in Fig. 3. Therefore, the oxygen consumption per unit weight of pregnant uterus remains fairly constant throughout the course of gestation.



cent (Table I). This patient had some respiratory difficulties during the procedure which might have contributed to the low oxygen saturation. Thus, despite the anesthesia, the arterial blood of these patients was fairly well oxygenated. The oxygen capacity of the blood varied between 14 and 17 ml. per 100 ml. with only one patient (No. 4) having values of 21 ml. per 100 ml. (Table I). Our values for oxygen saturation and capacity in pregnant women compare fairly well with those Barron<sup>13</sup> obtained in pregnant ewes.

Oxygen consumption of the pregnant uterus has been expressed in three different ways as in the case of uterine blood flow.

Total oxygen consumption calculated from the electromagnetic flow figures increased from 4.8 ml. per minute at 10 weeks to 22 ml. per minute at 28 weeks (Table I, Column 10, and Fig. 3).

Uterine oxygen consumption calculated from the N<sub>2</sub>O flow figures varied from 0.54 to 1.45 ml. per 100 grams per minute (Table I, Column 12, and Fig. 4). These figures were close to those Metcalfe and his associates<sup>11</sup> obtained in pregnancy at term and were slightly lower than our previous average of 1.9 also obtained at term with the same method.<sup>10</sup> As in the case of

blood flow, however, there was a marked variation in the individual values reported by us and by Metcalfe and his associates, and such a variation did not present a strict relationship with the duration of gestation (Fig. 4). We believe it to be due to the variability inherent in the N<sub>2</sub>O method of measuring flow. Hence, the oxygen consumption of the pregnant uterus per 100 grams of uterine weight remains constant throughout the period of gestation (Fig. 4). This fact is confirmed by the figures obtained from the 5 cases in which hysterectomy was performed. Uterine oxygen consumption calculated from the electromagnetic flow values and expressed on the basis of unit weight of pregnant uterus varied between 0.67 and 1.24 ml. per 100 grams per minute (Table I, Column 11). These figures were very close to those obtained with the N<sub>2</sub>O technique.

**II. The fetus.** Table II and Figs. 5 and 6 present the data obtained from the study performed on the fetuses. Because of the small size of the fetus prior to 12 weeks of gestation, the flow signal from the umbilical vessels was inadequate and collection of blood samples anaerobically was impossible. With the progress of gestation and increase in the weight of the fetus, the diameter of the umbilical vessels was larger but vaso-

Table II. Data on fetal blood flow, fetal oxygen saturation, and capacity and fetal oxygen consumption between 10 and 28 weeks of gestation

Patient	Length of gestation (weeks)	Fetal weight (grams)	Fetal blood flow (ml./min.)	Fetal blood flow (ml./100 grams/min.)	Fetal oxygen saturation (%)		Fetal oxygen capacity (ml./100 ml.)	Fetal oxygen consumption (ml./min.)	Fetal oxygen consumption (ml./100 grams/min.)
					Arterial	Venous			
1	10	75	—	—	—	—	—	—	—
2	12	90	8.5	9.4	—	—	—	—	—
3	14	98	—	—	—	—	—	—	—
4	14	100	11.0	11.0	55	40	17.5	0.3	0.30
5	15	120	15.0	12.5	52	37	15.8	0.4	0.33
6	16	118	15.0	12.7	—	—	—	—	—
7	16	108	12.0	11.1	57	42	18.2	0.3	0.28
8	16	200	22.0	11.0	55	40	21.0	0.7	0.35
9	17	250	28.0	12.2	60	45	17.0	0.7	0.28
10	19	290	30.0	10.3	58	35	17.5	1.2	0.41
11	24	500	60.0	12.0	61	42	19.8	2.3	0.46
12	28	650	80.0	12.3	65	45	22.0	3.5	0.54

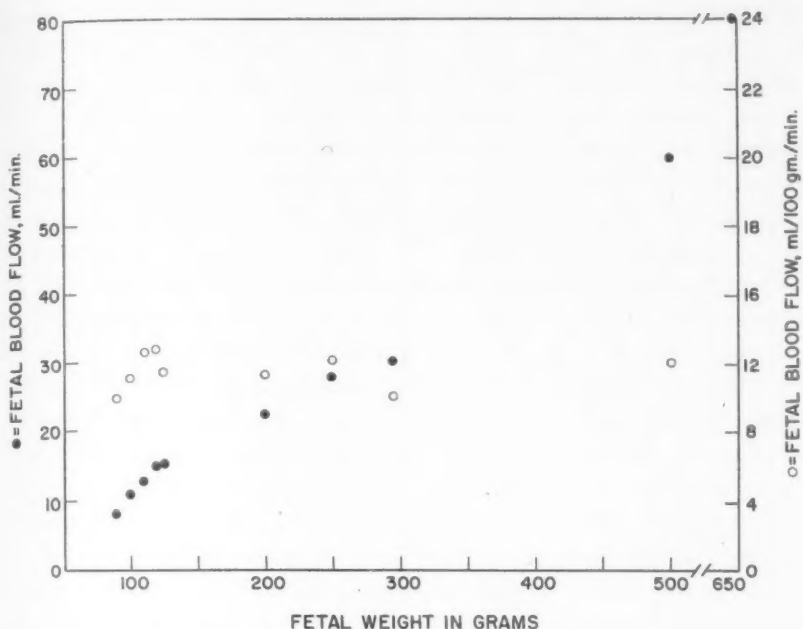


Fig. 5. Fetal blood flow obtained with the electromagnetic flowmeter placed around the umbilical vein. Total flow (black circle) increased from 8.5 ml. per minute in a 90 gram fetus (12 weeks) to 80 ml. per minute in a 650 gram fetus (28 weeks). Blood flow per unit of fetal weight (open circle) remained constant throughout gestation and averaged 11 ml. per 100 grams per minute.

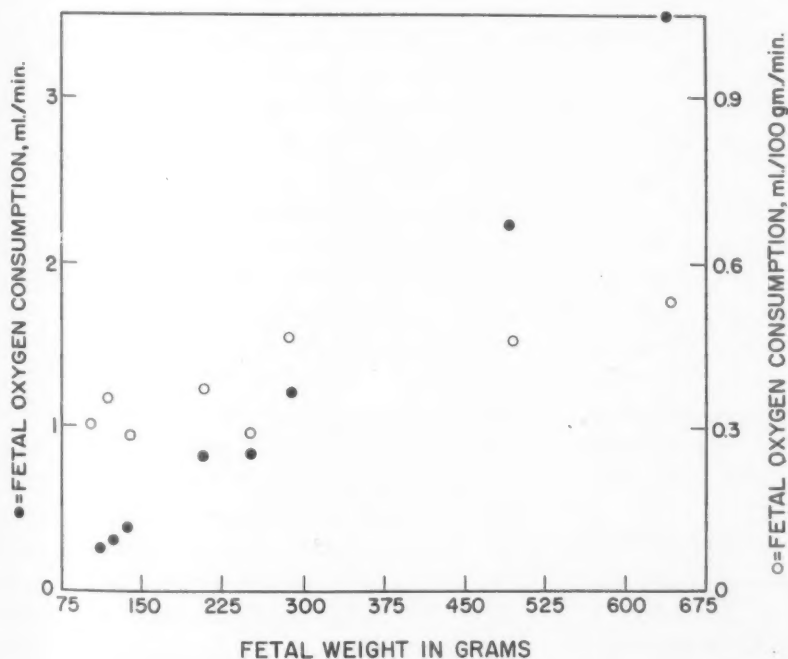


Fig. 6. Fetal oxygen consumption calculated from the umbilical flow and the arteriovenous difference of  $O_2$  as described under "Material and methods." Note the linear increase in total fetal oxygen consumption (black circles) as the fetal weight increased. However, fetal oxygen consumption per 100 grams of fetal weight (open circles) remained constant.

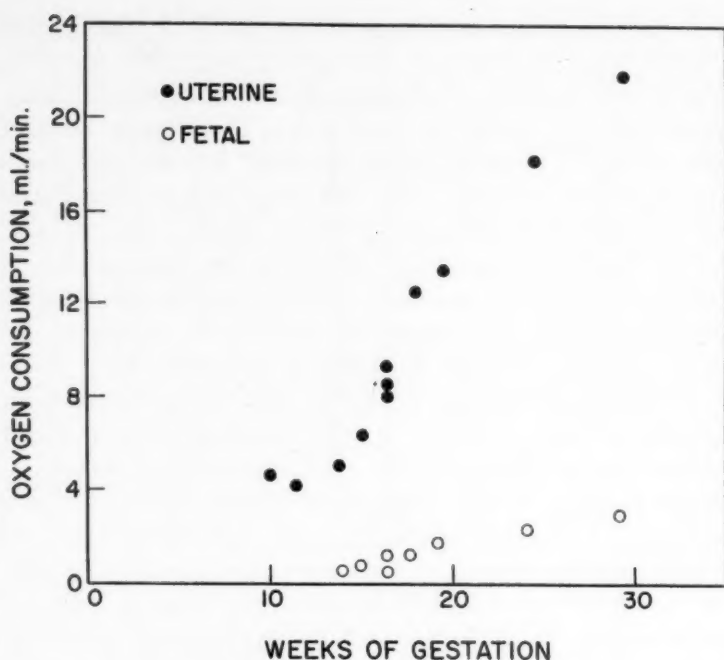


Fig. 7. In this figure, the values on total uterine blood flow are compared to those on fetal blood flow during the same periods of gestation. Note that both flows increased progressively and in a parallel fashion. However, the uterine blood flow was consistently higher than the fetal blood flow. We believe that the major portion of the total uterine blood flow is destined to the intervillous space.

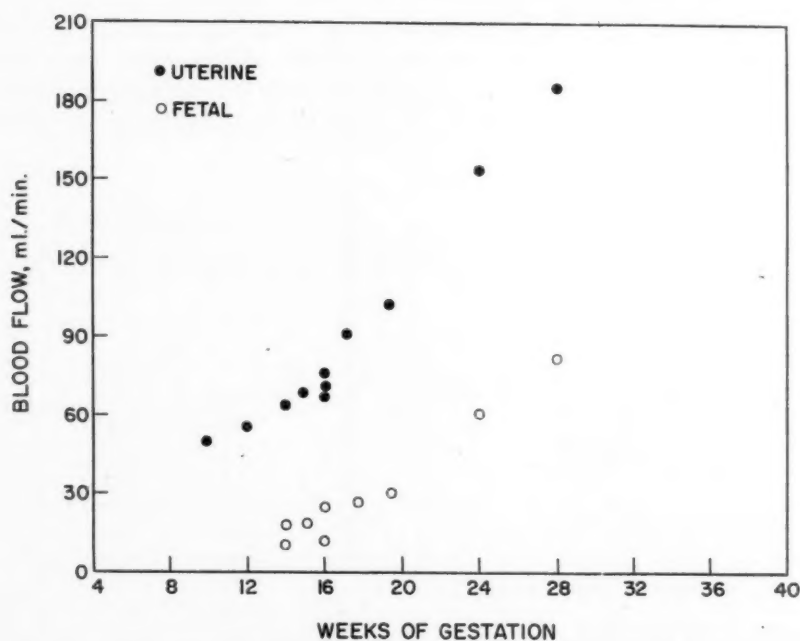


Fig. 8. Total oxygen consumption of the uterus is compared to that of the fetus. Note that although both increased progressively during pregnancy, the uterine oxygen consumption increased at a much faster rate than the fetal oxygen consumption, particularly after the sixteenth week of gestation. We believe that the placenta consumes the major portion of this difference.

spasm became a complicating factor which interfered with the study of some fetuses. Therefore, the figures on umbilical vein flow and particularly those on umbilical oxygen saturation and fetal oxygen consumption should be accepted as approximate values rather than the true values for the basal state in utero.

Umbilical vein flow increased from 8.5 ml. per minute at 12 weeks to 80 ml. per minute at 28 weeks of gestation (Table II and Fig. 5). During this same period, the fetal weight increased from 90 to 650 grams. Thus, there was a tenfold increase in the umbilical vein blood flow within 16 weeks of gestational growth. When computed on the basis of unit weight of the fetus, the umbilical blood flow remained constant and averaged 11 ml. per 100 grams per minute (Table II and Fig. 5). These figures agree very well with those of Acheson, Dawes, and Mott<sup>14</sup> and Cooper, Greenfield, and Huggett,<sup>15</sup> who measured umbilical flow in fetal lambs with entirely different techniques.

Arterial oxygen saturation (umbilical vein) varied between 52 and 65 per cent, and the venous saturation (umbilical artery) between 35 and 45 per cent (Table II). Fetal oxygen capacity varied between 16 and 22 ml. per 100 ml. of blood (Table II). These figures are in close agreement with those of others obtained from human gestation at term or just after delivery or from fetal lambs at various periods of gestation.<sup>14, 16, 17</sup> Total oxygen consumption of the fetus increased from 0.3 ml. per minute at 14 weeks in a fetus weighing 100 grams to 3.5 ml. per minute at 28 weeks in a fetus weighing 650 grams (Table II and Fig. 6). When calculated on the basis of unit weight, however, fetal oxygen consumption remained nearly constant and averaged 0.4 ml. per 100 grams per minute (Table II and Fig. 6). These figures agree fairly well with those Acheson, Dawes, and Mott obtained from the studies of fetal lambs.<sup>14</sup>

**III. Comparison of uterine and fetal values.** Figs. 7 and 8 compare the data on total blood flow and oxygen consumption of the

whole pregnant uterus to those of the fetus in the same patient. It can be seen that both uterine and fetal blood flows as well as uterine and fetal oxygen consumptions increased progressively and in a parallel fashion throughout pregnancy. At any given period of gestation, however, and particularly after the eighteenth week, the blood flow and oxygen consumption of the whole pregnant uterus were much higher and increased at a much faster rate than those of the fetus. This marked difference between the values of the fetus and those of the pregnant uterus cannot be accounted for solely on the basis of the need to supply the enlarging uterine mass itself. The largest portion of blood flow is probably destined for the placenta and intervillous space and is required to transport the essential elements for the growth of the fetus. This hypothesis is supported by the following evidence: (a) the greatest increase in uterine blood flow and oxygen consumption coincides with the greatest period of placental growth and at a time when the placental weight is larger than or equal to that of the fetus; (b) our previous studies<sup>18</sup> in pregnant sheep have shown that the blood flow to the pregnant uterus falls only slightly after the delivery of the fetus but decreases sharply after the expulsion of the placenta. The same reasoning applies to the striking difference in the rate of oxygen consumption which exists between the uterus and the fetus. It is expected that an organ which performs a multiplicity of functions, such as the placenta, would require a great amount of oxygen for its high metabolic activities. Such a high oxygen uptake by placental tissue has been observed in *in vitro* studies.<sup>19</sup>

#### Comment

It is generally believed that the fetus in utero lives in a hypoxic state. Barcroft<sup>20</sup> established the concept of "Mount Everest in utero" by which he compared fetal life to adult life at great altitudes. He based his concept on his findings of a low oxygen saturation and pressure in the cord blood



of fetal lambs and of other animals. Similar findings have been reported in humans and in animals by various investigators.<sup>21-24</sup>

Barcroft and his associates<sup>25</sup> attempted to study the circulatory adjustment of the pregnant uterus in animals. Although they used a somewhat crude technique, they were able to show that in the pregnant rabbit the blood flow and oxygen consumption of the uterus increased proportionally to the growth of the fetus.

The present data show clearly that in human subjects the circulation of the pregnant uterus adjusts itself effectively to the growth of the conceptual product. Up to the twenty-eighth week of pregnancy, the blood flow to the uterus increases progressively with the increase in the gestational age, and the increment is largely absorbed by the placenta. Whether the same rate of increase continues until the end of gestation cannot be stated from the present studies since no measurements were made after the twenty-eighth week. However, our previous studies<sup>18</sup> in pregnant sheep suggest that in the latter part of gestation the rate of increase in uterine blood flow is rather slow. Assuming that the same occurs in human pregnant subjects, then the blood flow to the uterus increases rapidly at the height of placental growth but would level off after the placenta had reached full maturity, which is supposed to occur near the thirty-third or thirty-fourth week of gestation.

The transfer of oxygen from the mother to the fetus across the placenta in the sheep has been studied by Barron.<sup>13</sup> He determined the oxygen saturation of the uterine and umbilical vessels in the same animal, and, by relating the saturation values to oxygen dissociation curves, he was able to establish an oxygen pressure gradient between the maternal and fetal blood. This pressure gradient tended to be greater at the arterial than at the venous ends of the placental capillaries.

Barron<sup>13</sup> further estimated the coefficient of oxygen utilization by the cotyledons and found it to be higher in twin pregnancy

than in single pregnancy. This coefficient of oxygen utilization gives a rough estimate of the oxygen lost to the uterine tissues and to the fetal blood, but gives no indication of the oxygen consumption of either the uterus or the fetus since it is not related to the blood flow. Nevertheless, Barron's findings of different values for single and twin pregnancies suggest that the larger the conceptual product, the more oxygen is required by the cotyledons.

The present studies, which deal with the amount of oxygen consumed by the whole pregnant uterus, confirm to a large extent those of Barron. The oxygen consumption increased markedly with the progress of gestation, particularly when the placental cotyledons were at their maximal growth. Evidently, the primary factor which secures this marked increase in the rate of oxygen consumption is the striking rise in uterine blood flow.

Although the studies on the fetus have been unanimous in showing a low oxygen saturation of the blood in the umbilical vessels, the values in the various series reported have varied markedly.<sup>16, 17, 21-24</sup> Under these circumstances, it has been difficult to analyze the adaptive mechanisms of the fetus to this hypoxic condition, particularly in view of the lack of adequate data which would correlate the low saturation with the fetal blood flow and oxygen consumption. Acheson, Dawes, and Mott<sup>14</sup> have recently found that in lambs the oxygen consumption of the fetus decreases markedly when the arterial saturation falls below 35 per cent. These observations suggest that the fetus in utero may maintain an adequate oxygen consumption provided its saturation does not fall below a critical level and this is achieved largely by an adjustment in the fetal blood flow.

Our data on early human fetuses agree very well with those of Acheson and his co-workers.<sup>14</sup> Total oxygen consumption of the fetus increased with the increase in fetal weight and the increase was due to a marked rise in fetal blood flow.

It should be realized, however, that even

under the best possible experimental conditions, measurements of the umbilical blood flow and umbilical blood oxygenation, particularly in early gestation, are subject to a variety of errors, some of which are as yet insurmountable. The small cardiac output of the fetus, the spasm of the umbilical vessels, the effect on the fetus of the anesthetic agents used in the mother, the effect of alteration in uterine tonus induced by surgical manipulation and by extravasation of the amniotic fluid on uterine and placental flow, the exposure of the fetus to the outside atmosphere—all these introduce errors in the determinations of blood flow and oxygenation of the fetus. It is probable, therefore, that most of the figures reported, including ours, do not represent the true picture of oxygen supply of the fetus in utero in a "basal" state. The fact that different investigators have obtained nearly similar values, particularly in regard to oxygen saturation in the umbilical vessels, does not prove that these values represent the true picture in utero. Analysis of the data reported by these investigators shows that practically the same techniques for obtaining blood samples were used and most likely the same errors were practiced. This hypothesis receives support from studies currently being performed in our laboratories.<sup>26</sup> Measurement of tissue oxygen tension with polarographic electrodes which do not require blood sampling have shown that the oxygen tension of the brain of the fetus in utero is equal to that of the mother. This finding seems to suggest that, despite the low oxygen saturation in the cord blood, the fetal tissues may not be as hypoxic as we have thought in the past and that the fetus seems to adjust itself fairly well to the so-called "Mount Everest in utero."

This adjustment becomes clearer when we compare our data (rough as these data may be) on blood flow and oxygen uptake of the fetus in utero to those reported in the literature on neonatal and adult life. Assuming, according to Dawes estimates,<sup>27</sup> that the figures on umbilical vein flow rep-

resent roughly 57 per cent of the total output of the ventricles the total cardiac output of the fetus in utero would be approximately 200 ml. per kilogram per minute. The cardiac output of the newborn infant measured by different methods<sup>28</sup> has been estimated to be close to 164 ml. per kilogram per minute and that of adult under basal conditions is approximately 62 ml. per kilogram per minute.<sup>29</sup> Therefore, the first mechanism of adjustment of the fetus to the low oxygen atmosphere is the tremendously high systemic flow which is three times that of the adult.

The second mechanism of adjustment is the higher extraction of oxygen of the fetus. While the arteriovenous oxygen difference of an adult life under basal conditions does not exceed 8 to 10, that of a fetus may be double or triple these figures.

The third factor is the higher oxygen capacity of the fetal blood. These three factors, together with the ability of the fetus for anaerobic metabolism, combine to protect and preserve fetal life against unfavorable environmental conditions.

#### Summary and conclusions

1. Uterine and fetal blood flow and oxygen consumption were studied in human pregnancy between 9 and 28 weeks of gestation.
2. Total uterine blood flow and total uterine oxygen consumption increased progressively throughout this period of gestation. However, when calculated on the basis of unit weight of pregnant uterus, the blood flow and oxygen consumption remained constant during the course of gestation.
3. The values for uterine blood flow obtained with the electromagnetic flowmeter were close to those obtained with the nitrous oxide method.
4. Umbilical blood flow and fetal oxygen consumption increased progressively with the increase in fetal weight and with the progress of gestation. When calculated on the basis of fetal unit weight, however, both flow and oxygen consumption remained constant.

5. At any given period of gestation, total uterine blood flow and oxygen consumption were higher and increased at a much faster rate than those of the fetus. Probably the difference between uterine and fetal values is largely absorbed by the placenta.

6. These findings are discussed in relation to their role in the various mechanisms

of adjustment of the fetus to intrauterine life.

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# Electrophoretic studies of serum proteins in pregnancy and the puerperium and in newborn infants

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THE blood proteins constitute a heterogeneous mixture of more or less related substances which vary qualitatively as well as quantitatively in different physiological states and in disease. Thus, Dieckmann<sup>1</sup> states that "there are undoubtedly changes in both the physical properties and chemical composition of albumin and globulin in pathologic conditions and in normal pregnancy."

Methods for the separation of various fractions, at first laborious, have gradually given way to techniques practical for the routine laboratory. Differential salting with sodium sulfate is commonly used to separate the blood proteins into an "albumin" fraction, which remains in solution, and a globulin fraction, which is precipitated. Tiselius, cited by Gray,<sup>2</sup> took advantage of the varying mobility of positively charged protein molecules in solution in an electrical field and recorded their movement optically. The photographed peaks repre-

sented concentrations of different protein fractions. In the late 1940's, the partitioning of a solution of proteins was simplified by the application of a standard current for a fixed period of time to solids such as paper, starch, glass powder, silica gel, etc., moistened with the protein solution. This permitted the measurement of the zones thus separated by colorimetric methods.

The present report is based on a study of the serum proteins during pregnancy and was stimulated by the observation of an unusual beta zone in the electrophoretically partitioned serum proteins from a pregnant woman.

## Review of the literature

Mack<sup>3</sup> summarized the literature with reference to the plasma proteins in pregnancy to 1955 and reported his own findings. He concluded that the plasma concentration of the total proteins and of the albumin and the gamma globulin fractions is reduced and that the alpha 1, alpha 2, fibrinogen, and beta globulin fractions are increased. He was unable to ascribe any significance to these observations in normal pregnancy or in the presence of toxemia.

Levy-Solal and Levy,<sup>4,5</sup> on the other hand, had previously called attention to a deformity of the albumin curve in the presence of toxemia. They interpreted their

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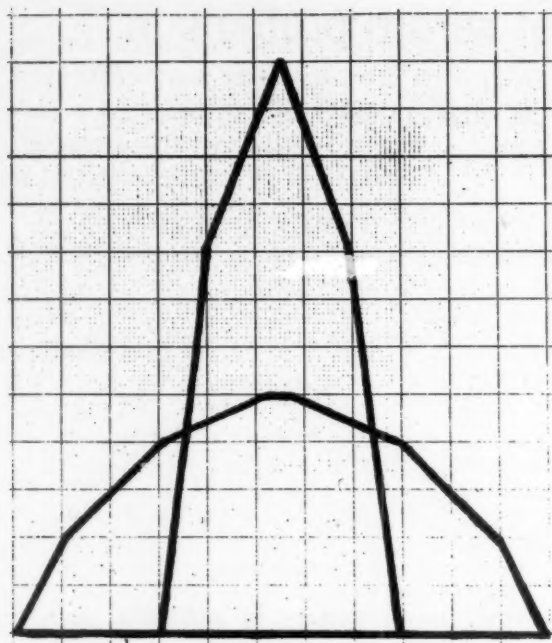


Fig. 1. Dissimilar curves subtend approximately equal areas.

findings as evidence of the presence of a protein peculiar to toxemia and called it "Compound X."

More recently, several reports of paper electrophoresis studies of the blood proteins during pregnancy have appeared in the French and Italian literature.<sup>6-10</sup> These several authors reported an increase in the beta or in the alpha 2 and beta globulin fractions of the blood proteins in normal pregnancy. Their findings in toxemia of pregnancy were not consistent.

#### Materials and methods

In the present study, serum proteins were fractionated on Whatman No. 3 MM paper strips in a Durrum type cell with barbital buffer (pH 8.6), with a current of 4.5 milliamperes for 18 hours, and dyed in bromophenol blue for 6 hours. The stained strips were scanned in the Analytrol R A densitometer by means of the B3 cam and a Corning blue glass filter (No. 5031). The total proteins were determined by the biuret method; 118 total protein determinations and protein fractionations were carried out

on the serum of 73 ante-, intra-, and postpartum women distributed as follows:

1. Eighteen patients between the seventh and fourteenth weeks of pregnancy. Twenty-five determinations were carried out on the serum from patients in this group, 3 determinations having been performed on one and 2 on each of 5 patients.

2. Twenty-one patients between the fifteenth and twenty-seventh weeks of pregnancy. Twenty-eight determinations were carried out in this group, 2 determinations having been performed on each of 7 patients.

3. Twenty-eight patients between the twenty-eighth and fortieth weeks of pregnancy. Forty-six determinations were carried out in this group including 6 determinations on one patient, 3 on each of 3, and 2 on each of 7 patients. One patient (M. S. 39) had been studied at 26 weeks, and the result of this determination is included in Group 2.

4. Eight women in labor. Five of these patients had been studied at least once between the twenty-eighth and fortieth weeks of pregnancy. The results of the earlier determinations are included in Group 3.

5. Nine postpartum patients. Eleven determinations were carried out in this group. One of these patients was studied 3 times in the postpartum period. Four of these patients had been studied antepartum, one ante- and intrapartum, and one was initially studied intrapartum. The ante- and intrapartum determinations are included with their respective gestational groups.

Similar studies were carried out on the cord blood of 10 newborn infants.

After 10 samples of serum from blood hemolyzed to varying degrees was studied, it became evident that hemolysis introduced an artefact of the beta zone and resulted in poor separation of alpha 2, beta, and gamma zones, rendering the results worthless. They were discarded.

Conventionally, the serum protein fractions have been expressed as grams per 100 c.c. of blood, or as per cent of the total based upon separation of the zones at the

lowest point in the valleys between the peaks. This technique ignores the form of the curve (Fig. 1). We, too, have quantitated the various fractions. However, in this report we have classified the curves on the basis of their forms because of an impression that this approach might be rewarding.

The form of the curves can be related to the relative heights of the 5 normal zones and the sharpness of the zone separation. In our experience the form of the albumin zone is predictable from the quantitative data and therefore nothing is gained by its descriptive classification. The alpha 1 fraction has not proved to be significant, in this study, either quantitatively or morphologically. Our data are reported in terms of the form of the beta zone and the relation-

ship between the height of the alpha 2, beta, and gamma globulin zones, and on the sharpness of the zonal separation.

Graphs were recorded on Spinco chart sheets, the smallest divisions of which are 1 mm. Peaks were considered to be of different heights if there was a difference of more than 3 divisions between the highest point of each peak. Poor separation of the alpha 2-beta zones was considered to be present when the depth of the intervening valley was less than 5 divisions below the alpha 2 peak.

### Results

The graphs were grouped into the following patterns (Fig. 2):

1. Gamma peak higher than or equal to the beta and alpha 2 peaks (Figs. 3-5).

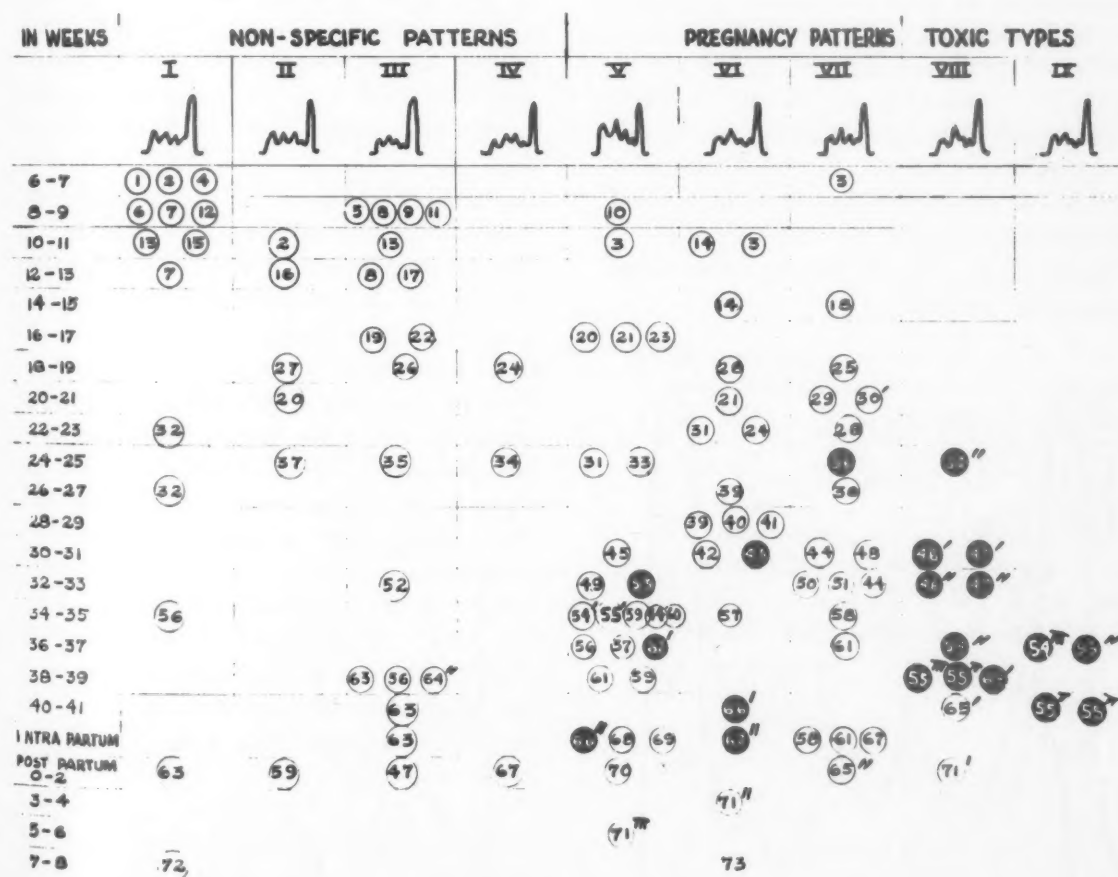


Fig. 2. Individual determinations arranged by weeks of gestation and grouped into 3 patterns which have been subdivided into groups. Black on white = normal pregnancy. White on black = toxemia and borderline toxemia.

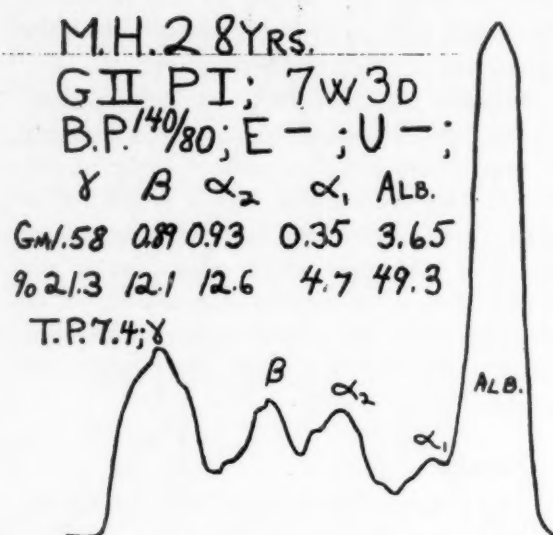


Fig. 3. Nonspecific pattern, alpha 2 and beta peaks of approximately equal height.

These are nonspecific patterns and were encountered in 18 of 25 determinations carried out on serum from women in the first trimester; 11 of 28 determinations carried out on serum from women in the second trimester; 6 of 46 determinations carried out on serum from women in the third trimester; one of 8 determinations carried out on serum from intrapartum patients; 5 of 11 determinations carried out on serum from postpartum patients.

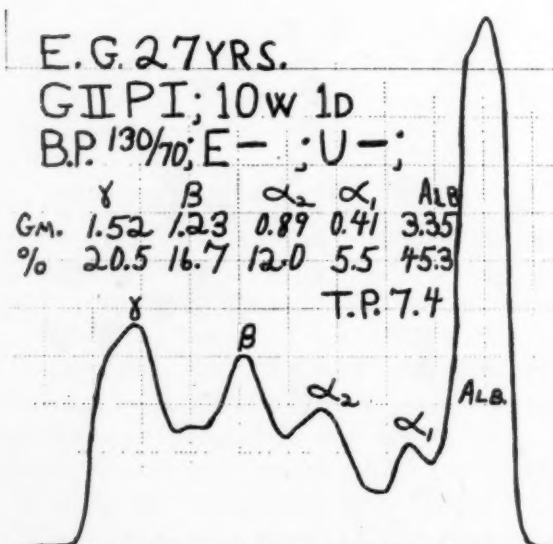


Fig. 4. Nonspecific pattern, beta peak higher than alpha 2 but less than gamma.

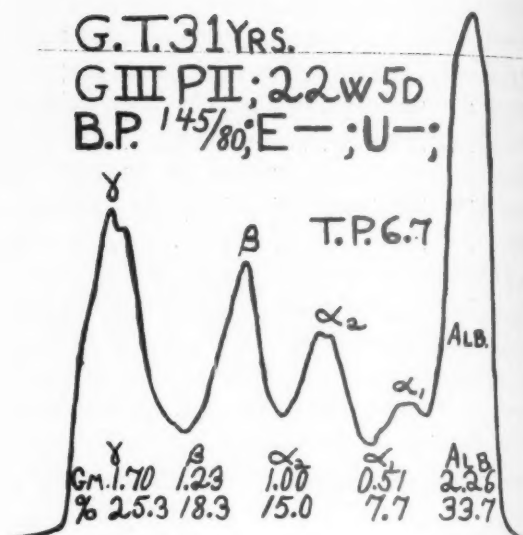


Fig. 5. Nonspecific pattern as for Fig. 4.

2. Beta peak taller than either the gamma or the alpha 2 peaks and the beta zone slender and symmetrical (Figs. 6-8). This pattern was encountered in 7 of 25 determinations carried out on serum from women in the first trimester; 16 of 28 determinations carried out on serum from women in the second trimester; 27 of 46 determinations carried out on serum from women in the third trimester; 7 of 8 determinations carried out on serum obtained intrapartum; 5 of 11 determinations carried out on serum obtained up to 7 weeks post partum. This pattern was sufficiently striking to be characterized as the pregnancy pattern.

3. Absence or loss of separation of the alpha 2 and beta zones (Figs. 9 and 10). This pattern was encountered in one determination carried out on serum in a woman in the twenty-fourth week of pregnancy; 13 (6 patients) of 46 determinations carried out on the serum of women in the third trimester; one determination carried out on serum from a postpartum patient.

Six of the 7 antepartum patients displayed clinical evidence of toxemia, or borderline\* toxemia. Five patients with clinical evidence of toxemia or borderline\* toxemia did not show this pattern.

\*Criteria of American Committee for Maternal Welfare.

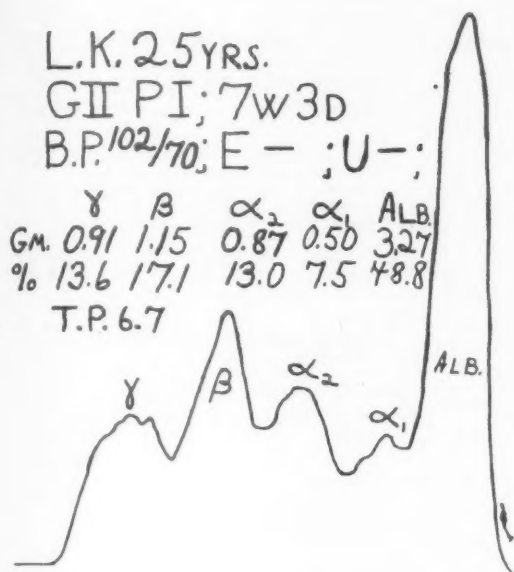


Fig. 6. "Pregnancy pattern," slender symmetrical beta peak; taller than gamma peak and significantly taller than alpha 2.

This pattern evolved from previously normal pregnancy patterns in 3 patients coincidental with clinical evidence of toxemia.

C. H. 54 (Figs. 11 and 12) is an example of a patient whose pattern converted from a tall beta peak with clear-cut alpha 2-beta

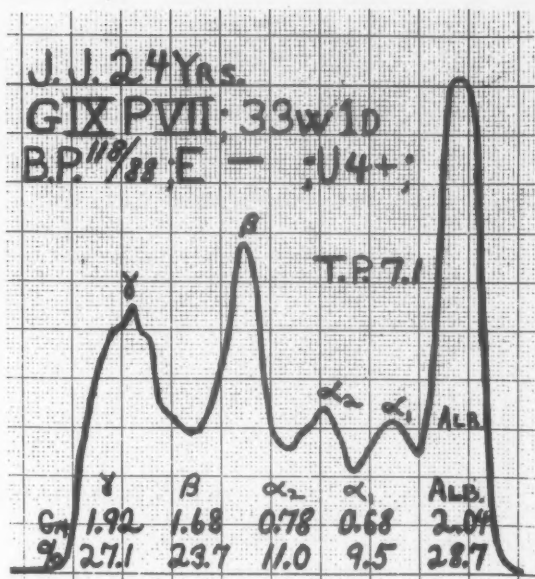


Fig. 8. "Pregnancy pattern" as in Fig. 6.

separation into a pattern lacking the alpha 2-beta separation but retaining the beta peak. These changes were coincidental with a weight gain of 5½ pounds in 2 weeks, a blood pressure shift from 120/70 to 136/80, and the development of 2 plus pitting edema.

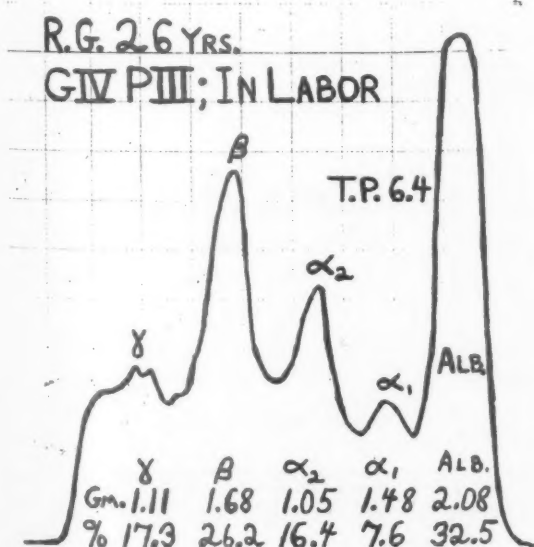


Fig. 7. "Pregnancy pattern" as in Fig. 6.

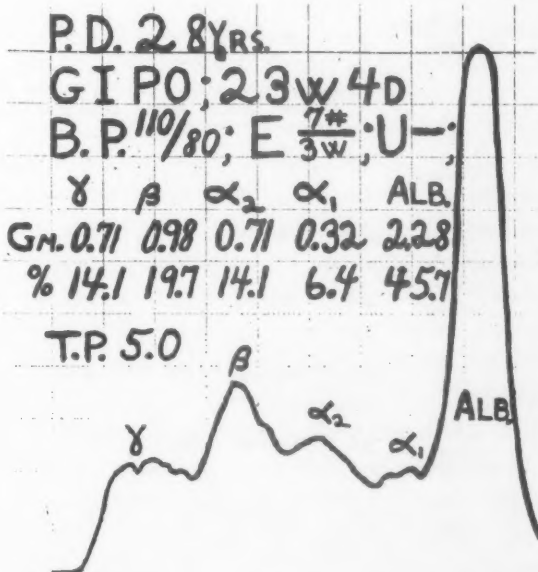


Fig. 9. Shallow valley between alpha 2 and beta peaks.




















TOXIC OR POTENTIALLY TOXIC PATIENTS WITH NORMAL PREGNANCY CURVES							
PATIENT & NO.	WEEKS OF GEST.	BLOOD PRESSURE	EDEMA	WEIGHT GAIN IN LBS PER WEEK	ALB.	GRAPH	REMARKS
N.C. (66)	40	140/100	+	-	0		HOSPITALIZED FOR TREATMENT OF TOXEMIA
J.U.J. (53)	33	118/88	0	-	4+		INITIAL CLINIC VISIT: HEMORRHAGIC CYSTITIS WITH GROSSLY BLOODY URINE. E. COLI CULTURED. TRACING DURING LABOR WITH NO SIGNIFICANT CHANGE.
Z.M. (62)	37	146/90	0	+1	0		ELEVATED BP WAS ONLY EVIDENCE OF TOXEMIA.
L.C. (43)	31	130/80	0	+5 1/2	0		WEIGHT GAIN ONLY EVIDENCE OF TOXEMIA
D.S. (36)	25	150/90	0	-	0		BP ELEVATED ON ONE OCCASION ONLY
NON TOXIC PATIENTS WITH "TOXIC" CURVES							
E.S. (65)	40	90/60	0	+1	0		POST PARTUM CURVE - NORMAL PATTERN
V.K. (71)	3RD DAY POST PARTUM	-	-	-	0		NO EVIDENCE OF TOXEMIA DURING PREGNANCY OR PUERPERIUM.
TOXIC PATIENTS WITH "TOXIC" CURVES							
D.L.W. (46)	31 & 32	132/94	2+	+2 1/2	0		
A.T. (47)	31 & 32	149/90	-	-	-		HOSPITALIZED FOR TOXEMIA
J.B. (64)	38	140/90	0	+2	0		TREATED FOR TOXEMIA
J.B. (64)	39	140/80	0	-1	0		
PATIENTS SHOWING CONVERSION FROM NONTOXIC TO TOXIC PATTERNS ASSOCIATED WITH CLINICAL EVIDENCE OF TOXEMIA							
R.D. (30)	20	120/70	0	-	0		
R.D. (30)	24	110/80	0	+3 1/2	-		DESCRIBED AS "MODEL" PATIENT WHO FOLLOWED DIET
C.H. (54)	34	120/70	0	+1 3/4	0		
C.H. (54)	36	136/80	2+	+2 1/2	0		
L.B. (55)	34	118/78	0	-	0		INITIAL VISIT TO CLINIC
L.B. (55)	37	144/100	3+	+5	TR.		HOSPITALIZED: RESPONDED; BP REMAINED ELEVATED AND PATTERN REMAINED ABNORMAL. SEE MASTER CHART.

Fig. 10. "Normal" pattern in patients with toxemia and instances of abnormal pattern.

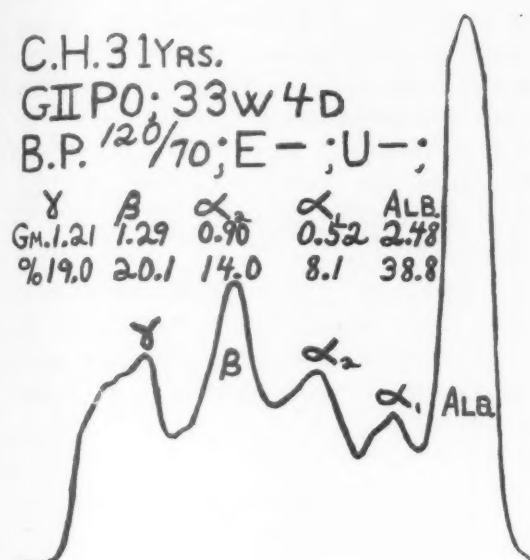


Fig. 11. Normal "pregnancy pattern," no clinical evidence of toxemia. (C. H., No. 54.)

The postpartum patient whose serum proteins presented this pattern was delivered of a male infant after an uneventful pregnancy. The infant had a hematocrit of 85 per cent, and he died. Detailed search for antibodies or incompatibilities between the mother's and baby's sera, and the father's and baby's cells yielded negative results. Autopsy failed to reveal an etiological factor for this neonatal death.

The tall beta peak and poor alpha 2-beta separation were encountered in one nontoxic patient (E. S. 65) at 39 weeks. It had returned to normal 9 days post partum.

The cord blood from 10 newborn infants was characterized by globulin levels consistently lower than the mother's and displaying a nonspecific pattern.

#### Comment

The silhouette as well as the percentile distribution and quantitation of the fractions of electrophoretically partitioned proteins is a composite of the concentrations of the numerous fractions, which go to make up the serum proteins, modified by the physical properties of the paper and the conditions under which the fractiona-

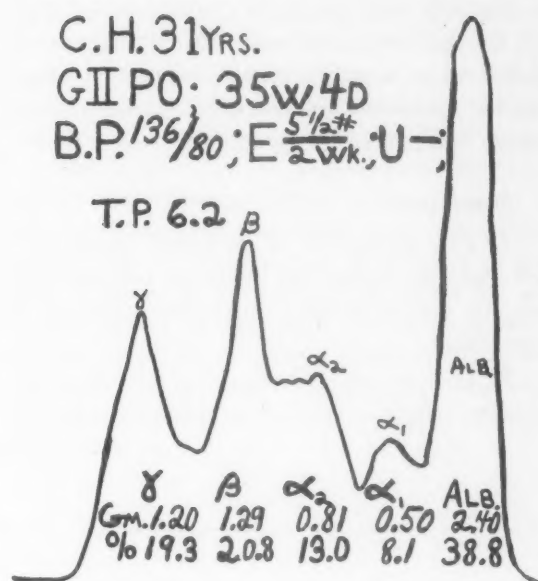


Fig. 12. Same patient as in Fig. 11, 2 weeks later.

tion was carried out. A characteristic of such a curve, which is present regardless of technique, may be significant.

The sharp, slender, beta globulin peak is striking in silhouette though not evident when the data are reported quantitatively. This "pregnancy" pattern is seen in curves obtained by a variety of techniques. Mack<sup>3</sup> suggested that the beta globulins play a role in the transport of lipids and perhaps other factors which are increased in pregnancy. This observation may account for the tall beta peak herein described.

Not only have we observed the "beta peak of pregnancy" but, based on the silhouette, have observed 2 other phenomena in studies of the curves obtained by electrophoretic partitioning of serum proteins from pregnant women:

1. Poor separation of the alpha 2 and beta zones is presumptive evidence of impending or present toxemia. This occurred in 6 of 11 patients with toxemia or with clinical features suggestive of toxemia.

2. Coincidental with the poor alpha 2-beta separation, the characteristic beta peak having been present is frequently lost or markedly altered. Such changes were seen in L. B. 55, P. D. 30, and C. H. 54.

Pardelli and Turchetti<sup>8</sup> published a graph of the electrophoretically partitioned serum proteins of a patient with toxemia of pregnancy without specifically characterizing these features of the graph.

### Summary

1. The silhouette of proteins partitioned by electrophoresis has features not brought out by percentile or quantitative methods of reporting.

2. The serum proteins in normal pregnancy fell into (a) a nonspecific pattern

which occurred with decreasing frequency as pregnancy progressed; and (b) a pattern characterized by a tall, slender, beta peak which occurred with increasing frequency as pregnancy progressed.

3. A curve in which the alpha 2 and beta zones are poorly separated. This pattern is strongly suggestive of toxemia of pregnancy.

4. In our material a significant shift away from the pregnancy curve characterized by a tall, slender, beta peak, once that form has developed, was suggestive of impending toxemia.

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### Discussion

DR. HENRY A. TELOH, Evanston, Illinois. Electrophoretic methods of analysis are relatively new in the diagnostic armamentarium of the clinical laboratory and, therefore, there are a good many things we do not know about this particular method of analysis.

In order to interpret electrophoretic patterns of this nature intelligently, one must take into consideration any number of metabolic changes which occur in blood during pregnancy and changes of a similar nature which may occur in other tissues. In attempting to analyze the types of curve obtained in this study one must consider first nonspecific changes. To reiterate what was said in the paper, there are changes which occur in pregnancy which are relatively nonspecific and which consist of a slight drop in the gamma and albumin fractions and an increase in alpha 1, alpha 2, and beta fractions. This drop in the albumin fraction can represent about 7 per cent and at times as much as 20 per cent of the total. When one considers this

decrease in albumin and gamma fractions, one begins to realize that an increase in other fractions is relative rather than absolute.

In order to try to analyze what happens in pregnancy, we had better forget about a discussion of proteins and concentrate on the lipids. To those of you who may be surprised at this statement, let me point out that in our present concepts of chemistry we consider cholesterol as one of the end products of chemical manipulation of macromolecular particles consisting principally of lipid and protein in combination. One must also realize that during our handling of serum we break down larger components into smaller components and come up with a thing called cholesterol. Lipids do not occur as such in the blood stream in great number but occur in combination with other components, particularly protein.

We must then consider what occurs in electrophoretic analysis of these lipoproteins. In general, there are two groups: the alpha and the beta lipoproteins. The second major division,

the beta lipoproteins, falls into the group occupied by the beta globulins. There is a smaller fraction which in the normal individual is very small and follows alpha 2. Taking this into consideration, what are the alpha globulins? They consist of a protein combined with smaller lipid particles. The beta globulins contain a larger lipid component including most of the cholesterol. Taking this into consideration, under what conditions do we find an increase in beta globulins? We find them especially in those cases in which there is an increase in cholesterol: hypercholesteremia, the nephrotic syndrome, uncontrolled diabetes, myxedema, and, as indicated,

in pregnancy. An increase in the beta fraction is common to all these conditions and is apparently associated with an increase in blood cholesterol. Dieckmann, in his book indicated the changes that occur in pregnancy. The serum cholesterol levels in the nonpregnant were 175, in the first trimester 270, at term 331, and 8 weeks post partum 254. What does this mean? It is logical to assume that an increase in the beta globulin is a manifestation of or an accompaniment of the high serum cholesterol which occurs in pregnancy. How can this be proved? It will take considerable more work, and I am afraid would require ultracentrifugation methods.



# Lactic dehydrogenase in pregnancy and the puerperium

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THIS study was undertaken to establish the effect of normal pregnancy, labor, and the early puerperium on serum lactic dehydrogenase levels.

One of the most promising of the serum enzyme studies recently introduced into clinical work is lactic dehydrogenase (LDH), a glycolytic enzyme widely present in body tissues and fluids. Serum elevations of this enzyme have been of notable use in the diagnosis of myocardial infarction. In equivocal cases, LDH has proved superior to the transaminase determination, since LDH elevation persists for a significantly longer period of time after the initial necrosis.<sup>1</sup>

LDH has frequently been noted to be elevated in the leukemias, particularly acute leukemia and chronic myeloid leukemia. West<sup>2</sup> found that the LDH levels appeared to be related to the clinical status of the disease. In the same leukemias, Bierman<sup>3</sup> has described elevated LDH activity in 84 of 85 untreated patients, while all determinations in 6 patients under active therapy were within normal limits. In the same series, 7 leukemic patients were studied serially, and a good correlation was found between clinical status and LDH levels, elevations being associated with increase in the number of immature cells in the bone marrow and with a falling hemoglobin and platelet count.

The activity of this enzyme in serous effusions and in cerebrospinal fluid has also been studied.<sup>4</sup> In serous effusions LDH activity is less than that of the serum, unless malignant cells are in contact with or in suspension in the fluid. The elevated values found in malignant effusions furnish a supplemental aid to cytological studies. Similarly, in cerebrospinal fluid, elevations are frequent in metastatic disease, while normal values are the rule in primary malignancy. Elevated LDH has also been noted to be relatively frequent in skeletal muscle damage, liver disease, lymphomas, disseminated carcinoma, and intravascular hemolytic episodes.

The large number of conditions which have been reported to alter LDH activity in serum indicates the need for a broad survey of all conditions which affect this determination. The ultimate status of this promising test must await careful study of the influence of a wide variety of states of health and disease on serum LDH. The influence of normal pregnancy on LDH activity has been variously reported, both normal and elevated values having been found. These will be discussed in relation to our own data.

## Methods and materials

All determinations were done on serum from clotted venous blood. Determinations of LDH activity in most specimens were made within a few hours, the remainder

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being refrigerated at  $-20^{\circ}$  C. until the test was performed. Care was exercised in the handling of all specimens to prevent erroneous elevations due to hemolysis, and all grossly hemolyzed specimens were discarded. In addition, in those patients with questionable hemolysis, in whom elevated values were obtained, repeat blood testing was done within a short period, usually less than 96 hours. If found normal, the previously elevated values were discarded from the study. In 2 patients with elevated values, retesting was not possible, and these results are included in the study.

The patients ranged in age from 15 to 41 years. Ninety-one patients were utilized in the study of LDH in normal pregnancy, and a total of 120 determinations were made, including the 2 elevated values previously mentioned. The specimens were drawn during the last 7 months of gestation, and in a few patients serial specimens were obtained in 3 consecutive months.

Forty-one patients were studied in labor, delivery, and the puerperium. Specimens were taken in active labor, immediately after delivery, and at 12 hours, 24 hours, and 4 days post partum. Complete serial specimens were available in 20 patients, and a total of 154 determinations were obtained.

LDH determinations done at delivery and in the puerperium are subject to at least one possible source of error, the probable liver cell damage associated in some degree with all volatile anesthetic agents. To aid in ruling out hepatic origin for LDH elevations, serum glutamic pyruvic transaminase determinations were done on 55 of the 154 blood specimens.

Serum LDH was determined by use of the spectrophotometric method of Wroblewski and LaDue.<sup>5</sup> In our own laboratory, serum values in a comparable nonpregnant female control group ranged up to 680 units per milliliter of serum, coinciding with the upper level of normal of Wroblewski.

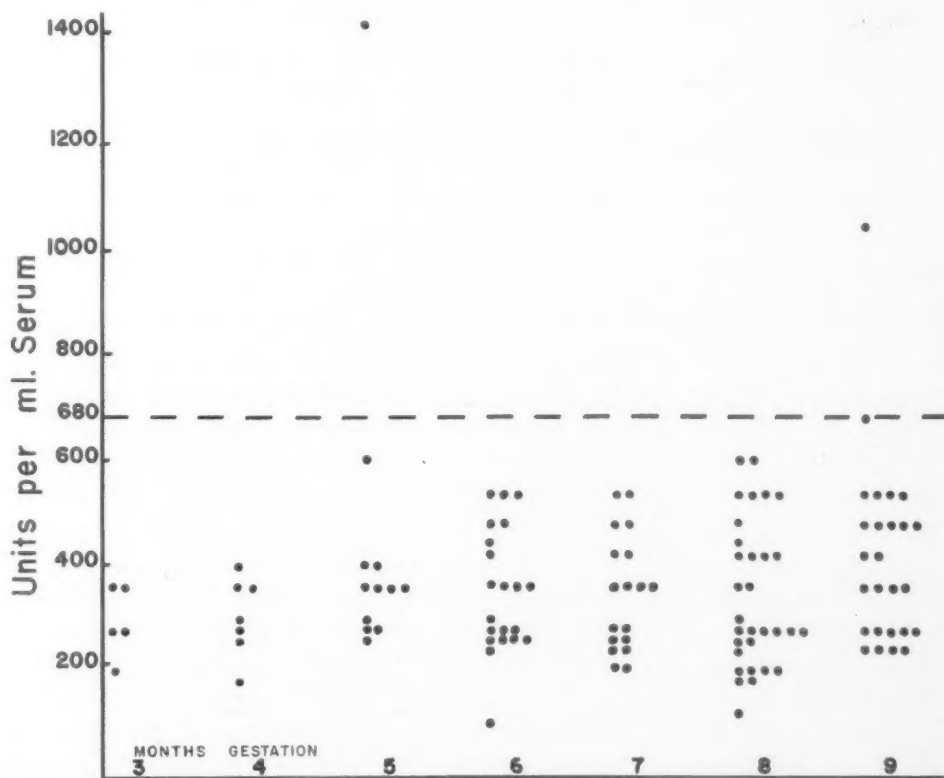


Fig. 1. Serum LDH levels during normal pregnancy.

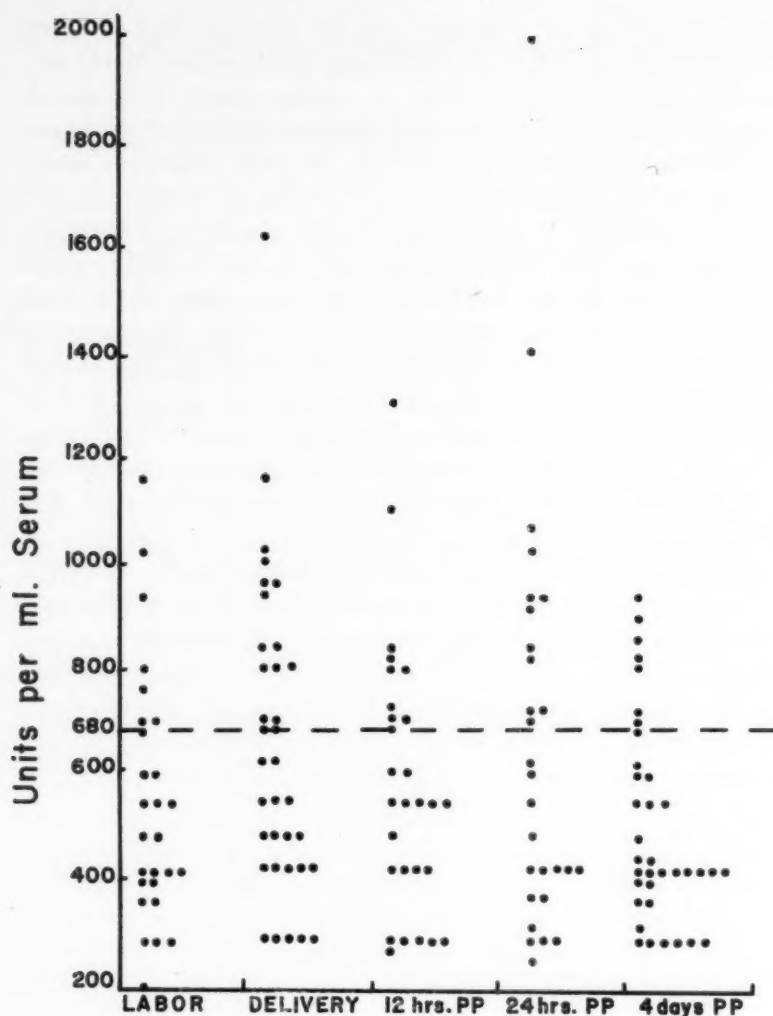


Fig. 2. Serum LDH levels.

### Results

**Serum LDH in pregnancy.** One hundred and thirty-two determinations were performed on 91 patients during the last 7 months of gestation. Twelve of the specimens were either grossly hemolyzed or were discarded because early repeat determinations were completely within normal limits. Two other elevated values were obtained, one in the fifth month and one in the ninth month of gestation. These determinations could not be checked and hence are included with the 118 normal values in Fig. 1.

From the values plotted on the scattergraph, it is apparent that neither normal pregnancy, nor any period thereof, causes elevation of serum LDH activity (Fig. 1).

**Serum LDH in labor, at delivery, and post partum.** Fig. 2 presents the LDH determinations taken in active labor, in the delivery room immediately after delivery, and at 12 hours, 24 hours, and 4 days post partum. Forty-one patients were studied and a total of 154 determinations were performed.

In active labor, approximately 25 per cent (7 of 27) determinations revealed elevations, as did 40 per cent (14 of 35) at delivery, 33 per cent (9 of 29) at 12 hours post partum, 44 per cent (12 of 28) at 24 hours post partum, and 20 per cent (7 of 36) at 4 days post partum.

The configuration of this scattergraph

suggests a curve reaching its peak between delivery and 24 hours post partum and tapering toward normal on the fourth postpartum day. In 20 patients serial determinations were available, and the curves obtained were consistent with this suggested curve.

Serum glutamic pyruvic transaminase determinations were done on 55 of the 154 blood specimens in this group, including 11 labor, 16 delivery, 10 twelve-hour, 11 twenty-four-hour, and 7 four-day postpartum specimens. Only 2 slight elevations were found, both of which were associated with normal LDH levels. These findings suggest that the LDH elevations found are not attributable to liver cell damage due to anesthesia. This fact is supported by the finding in 2 patients in whom pudendal block was the only anesthetic agent used, and in whom similar LDH curves were obtained.

#### Comment

The present investigation indicates that serum LDH values remain normal in the uncomplicated pregnancy.

Some studies are in disagreement with this conclusion. Hill<sup>6</sup> found elevated values in approximately one half of 40 determinations done during pregnancy, but the stage of gestation and the degree of elevation are not stated. More recently Knutson<sup>7</sup> reported slight elevations (up to 15 per cent above normal levels) in 7 of 100 patients, and Hagerman<sup>8</sup> states that LDH activity is normal in the first 34 weeks of gestation but then rises steadily in the last 6 weeks, reaching at term an average value of 50 per cent above normal levels. Nevertheless, the majority of previous studies of this enzyme in normal pregnancy report no elevation of LDH. West<sup>9</sup> has reported normal values during pregnancy in 70 women, while Smith<sup>10</sup> reports 100 normal determinations, and Little<sup>11</sup> recently has stated that in 75 determinations done during normal pregnancy, all values were within normal limits.

Previous studies which have included determinations of LDH in labor have indicated elevated values in 25<sup>11</sup> to 40 per cent<sup>9</sup>

of patients, and our 25 per cent elevations in labor are in close agreement with these. In the present study this elevation is seen to persist and increase through the time of delivery, when 40 per cent of patients reveal elevated serum LDH, and then to gradually taper off and approach normal at 4 days post partum. These elevations do not seem to be attributable to anesthesia associated with delivery.

Indeed, it should not be surprising to see elevation of serum LDH levels during this period of physiological upheaval and dynamic involution. Specific reasons for these elevations are not forthcoming. Two possible explanations are readily apparent—the element of intravascular hemolysis in uterine sinusoids and the active involutional changes of the uterus, with reduction of the protoplasmic mass.

Postpartum LDH determinations have been reported only in the past year, the largest series consisting of 15 determinations done during the 5 days immediate post partum, in which all determinations were found to be elevated.<sup>10</sup>

The question remains as to whether LDH may be of more specific value in the diagnosis of obstetrical complications. Little,<sup>11</sup> in his recent excellent study of LDH as related to placental deficiency, found a high degree of correlation between elevated LDH in labor and the incidence of placental infarction and fetal distress. Moreover, in 7 patients with abruptio placentae, elevated LDH was obtained in 6 prior to delivery, and the elevation seemed to correlate well with the amount of retroplacental clot present. This is the first study to indicate possible valuable uses for LDH determinations in obstetrical complications of pregnancy.

In our small number of patients (7) who had elevated serum LDH during labor, confirmation of placental insufficiency as a cause for these elevations was not possible. No fetal distress was apparent, and in no instance was cry or respiration depressed. The average birth weights of the 7 babies delivered from parturients with elevated LDH did not differ significantly from that



of the remaining 20 infants. Although placentas were not sectioned routinely, no gross infarcts were apparent.

### Summary

1. Serum LDH activity has been studied during the course of 91 normal gestations. One hundred and twenty determinations were made during the last 7 months of preg-

nancy, and consistently normal serum levels are present.

2. Elevated LDH activity is present in labor, at delivery, and in the early puerperium, and this elevation appears to bear no relation to anesthesia.

We wish to express our gratitude to Mrs. Monica Machina and Miss Marjorie Jacobson for technical assistance.

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# Vitamin B<sub>12</sub> absorption during pregnancy: a controlled study

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IN RECENT years, there has been an increasing amount of investigation into vitamin B<sub>12</sub> absorption in the human being. Hellegers and associates have shown that vitamin B<sub>12</sub> absorption normally is increased during pregnancy, although studies by Boger and co-workers,<sup>2</sup> as well as others,<sup>3</sup> describe a progressive decrease in B<sub>12</sub> levels during gestation. It has been shown that the fetus at birth has a serum B<sub>12</sub> level twice that of the mother.<sup>4</sup> Several cases of cretinism have also been reported in which the mothers had low B<sub>12</sub> levels in addition to hypothyroidism.<sup>1</sup> These facts stimulated us to investigate the hematological and clinical response of the normal pregnant patient to oral B<sub>12</sub> therapy. In this study we measured the plasma B<sub>12</sub> levels of: (a) pregnant patients treated with oral B<sub>12</sub> and D-sorbitol, and (b) plasma B<sub>12</sub> levels in a placebo group. In addition, we compared both groups to determine whether any demonstrable benefit was conferred on the patients treated with oral B<sub>12</sub>.

## Method

Forty-six women were given oral B<sub>12</sub> or a placebo from the first or early part of the second trimester of pregnancy until the third day post partum. Twenty-two patients were given 25 mcg. of oral B<sub>12</sub>\* and 11 Gm. of D-sorbitol\* daily. The latter is a crystalline hexahydric alcohol, which has been

shown to increase vitamin B<sub>12</sub> absorption.<sup>5-8</sup>

Twenty-four patients received an inactive placebo containing glucose with water and citric acid. Blood samples were drawn monthly and post partum. Plasma B<sub>12</sub> levels were determined by microbiological assays with use of *Lactobacillus leichmanii* No. 7830. Hemoglobin, hematocrit, and red cell determinations were made initially, 6 weeks before delivery, and 3 days post partum. Other observations recorded were: length of labor, blood loss, edema, weight gain, complications of pregnancy, and subjective symptoms. All patients in both groups were given routine oral iron therapy, but no vitamin supplement other than vitamin B<sub>12</sub> was given.

## Results

Administration of vitamin B<sub>12</sub> produced a definite increase in B<sub>12</sub> plasma levels above those of the control group, as can be seen from Fig. 1. This increase was most marked immediately following the start of B<sub>12</sub> administration and consistently remained above pretreatment and control group levels. Both groups exhibited a trend toward lower B<sub>12</sub> levels as pregnancy progressed; however, approximately 4 to 6 weeks ante partum, a sharp rise occurred and continued throughout the immediate postpartum period.

Blood tests revealed that the red cell count, hemoglobin level, and hematocrit count of patients in both groups had fallen

\*As components of Vi-Sorbin, supplied by Smith Kline & French Laboratories.

Table I. Objective and subjective response

	Vitamin B <sub>12</sub> group	Placebo group
Length labor (average)		
Primipara	10 hr., 20 min.	8 hr., 40 min.
Multipara	5 hr., 24 min.	3 hr., 50 min.
Mild to heavy blood loss	24%	28%
Edema	19%	42%
Weight gain (average)	18 pounds	19 pounds
Pre-eclampsia	0%	8% (2 patients)
Nausea	19%	29%
Indigestion	19%	21%

slightly during pregnancy and had risen again post partum (Fig. 2). No significant difference in either the downward or the upward phase of the blood picture was noted between the control and the placebo group. In both groups, the length of labor, postpartum blood loss, weight gain, and subjective symptoms were essentially similar (Table I). There was, however, a two to one ratio of occurrence of edema in the placebo group (42 per cent) compared to the vitamin B<sub>12</sub> group (19 per cent). Seven patients in the placebo group and 5 in the drug group received diuretics following unusually rapid and excessive weight gain.

Comment

The preceding data confirm the findings of other investigators that plasma B<sub>12</sub> levels during pregnancy can be significantly elevated by oral therapy. Chow and associates<sup>7</sup>

reported a marked elevation of vitamin B<sub>12</sub> levels following intramuscular and oral (with D-sorbitol) B<sub>12</sub> administration. The elevations observed in the present study are by no means as marked or consistent, but the adjusted averages do show an increase of approximately 100  $\gamma\gamma$  per milliliter following oral vitamin B<sub>12</sub> administration. The second rise in plasma B<sub>12</sub> levels at 34 to 36 weeks of gestation—following the sharp rise immediately after the onset of therapy—is of special interest. It is possible that this second rise may have been due to the “lessened hemodilution” which normally occurs in the cardiovascular system in the last trimester of pregnancy.<sup>9</sup> This possibility is further strengthened by a similar occurrence in the placebo group. The B<sub>12</sub> rise seen in the last trimester contrasts with the progressive decrease throughout pregnancy seen in other studies.<sup>2, 3</sup> Erdberg,<sup>10</sup> in addi-

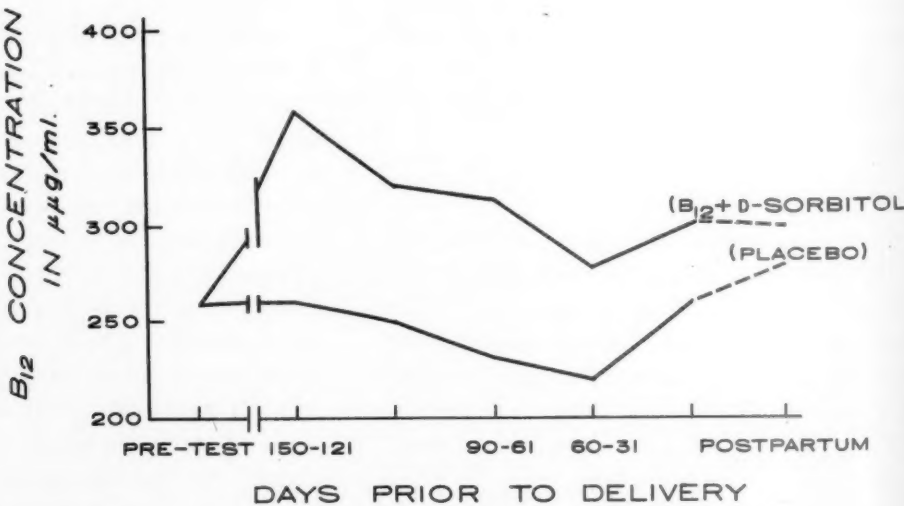


Fig. 1. Average plasma B<sub>12</sub> response in 46 pregnant patients.

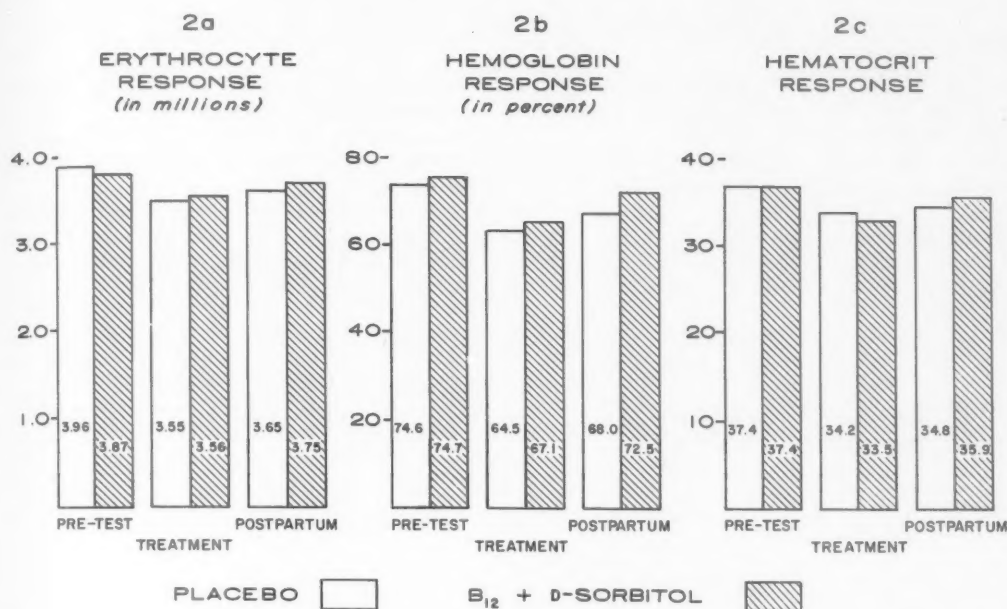


Fig. 2. Average erythrocyte, hemoglobin, and hematocrit response to B<sub>12</sub> and placebo therapy, by 46 pregnant patients.

tion, has reported a postpartum decrease in the B<sub>12</sub> levels, but his patients also received folic acid, making a comparison difficult. This third trimester rise, perhaps, could partially explain the much greater response of Chow's patients who were treated only during the last 6 weeks of pregnancy.<sup>7</sup>

One factor worthy of further investigation is the lesser edema seen in the drug group. One wonders whether the B<sub>12</sub> and/or D-sorbitol were the principal factors causing a diminution of edema. D-sorbitol, in addition to its ability to increase B<sub>12</sub> absorption, has laxative and humectant qualities.<sup>11</sup> It is also interesting to note that the only patients to develop pre-eclampsia were in the placebo group. While the size of the sample is too small to make this difference statistically significant, further investigation with larger numbers of patients should clarify the relationship, if there is one, between B<sub>12</sub> levels, D-sorbitol, and fluid retention.

The study showed no significant alterations in the hematological picture as a result of B<sub>12</sub> therapy. Although the value of B<sub>12</sub> to the pregnant woman is yet to be ascertained, this study has proved that B<sub>12</sub> levels throughout pregnancy can be main-

tained above pretreatment levels by oral therapy.

#### Summary and conclusion

1. Plasma vitamin B<sub>12</sub> levels in 46 patients were determined throughout pregnancy. Twenty-two patients were given 25 mcg. of vitamin B<sub>12</sub> and 11 Gm. of D-sorbitol, orally, daily; 24 patients were given an inactive placebo.

2. Following therapy, plasma B<sub>12</sub> levels in the study group were consistently higher than in the placebo group.

3. Oral administration of vitamin B<sub>12</sub> with D-sorbitol can substantially increase plasma vitamin B<sub>12</sub> levels.

4. The vitamin B<sub>12</sub> levels throughout pregnancy are graphically demonstrated; the sharp rise in the last month is thought to be partially due to the "lessened hemodilution" of the vascular system.

5. The possibility that vitamin B<sub>12</sub> and/or D-sorbitol play a role in preventing water retention is briefly discussed; further investigation should be undertaken to clarify this question.

6. The value of supplementary vitamin B<sub>12</sub> therapy for the normal pregnant patient is not yet known.



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## Studies in placental permeability

Transmission of poliomyelitis antibodies, lipoproteins,  
and cholesterol in single and twin newborn infants

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IN PREVIOUS papers, we have compared the electrophoretic pattern in parturient and cord blood in normal and in pathological pregnancies.<sup>1</sup> There is a significant increase of the relative level of fetal  $\gamma$  globulin as compared to the maternal  $\gamma$  globulin level. This *relative hypergamma-globulinemia* of the newborn has been considered as an indication of its physiologic maturity. Transfer of the maternal  $\gamma$  globulin to the fetus starts toward the sixth month of the pregnancy; its rate is different from that of the other serum proteins. Indeed, whereas the albumin and the other fractions are transferred at approximately the same rate throughout the last trimester, the rate of transfer of the  $\gamma$  fraction is very low at the beginning (16 to 20 per cent of the maternal value), but it increases sharply and reaches the maternal level during the eighth month; the fetal level then exceeds the maternal level, so that at term the ratio of fetal/maternal  $\gamma$  globulin is 1.35-1.50.

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After birth, the  $\gamma$  globulin level of the infant's serum diminishes gradually and reaches its lowest level toward the fourth month, when the infant apparently starts to elaborate its own  $\gamma$  globulins. This cycle allowed us to establish an index of physiological prematurity, sometimes different from the chronological or the weight criterion: a relative hypogammaglobulinemia of less than 0.7 might be considered as an indication of prematurity, at least as far as the immune protection processes are concerned. Fig. 1 gives the comparative values of serum proteic fractions in mother and newborn in full-term and premature infants at various ages, while Fig. 2 schematizes the life cycle of the  $\gamma$  globulins in terms of the ratio of fetal/maternal  $\gamma$  globulin.

The F/M (fetal/maternal) ratio for  $\gamma$  globulin might also be an indication of physiological postmaturity; indeed there might be a relative hypogammaglobulinemia indicating either an alteration of placental permeability or decay of the already transferred  $\gamma$  globulin. Work is in progress to determine the validity of this hypothesis.

This selective permeability of the placenta for the  $\gamma$  globulins is apparently part of the mechanism of passive protection in the early months of life. Although the nature of the transferred  $\gamma$  globulins is incompletely known, numerous investigations have established the transfer of various antibodies—

pertussis, autoantibodies, etc.<sup>2-4</sup> The problem of the placental transfer of poliomyelitis antibodies presented a special challenge, owing to the recent mass vaccinations. We hoped to time the vaccination of the pregnant woman so that the highest titer of maternal antibodies would coincide with the moment of maximum rate of transfer of the  $\gamma$  globulins through the placenta. This in its turn should ensure the highest level of protecting antibodies in the newborn and therefore longer protection of the infant.

Six pregnant women were vaccinated at various stages of pregnancy and the titer of neutralizing antibodies was determined before term and during and after parturition.

The comparative data of the antibody levels are presented in Fig. 3.

The half life of the infant's antibodies has been estimated as being approximately 55 days; this will offer 4 to 6 months' protection in a newborn with a high initial titer, provided that the titer of neutralizing antibodies determined in our experiments reflects the actual level of protecting antibodies. The gradual decrease in antibody titer is an indication that during the first months of life the infant is incapable of elaborating its own antibodies. Comparison between the antibody titer and the level of the total  $\gamma$  globulin in infants failed to show any significant correlation between these 2

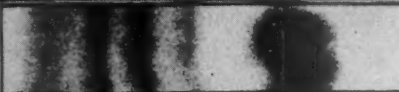
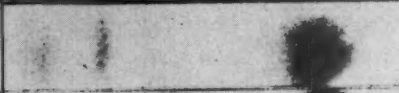

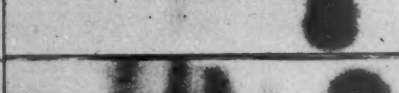
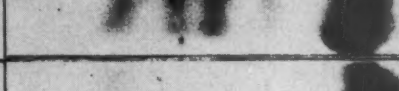
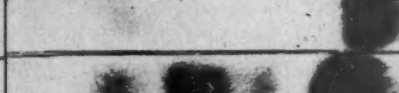
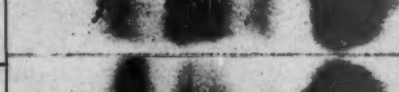
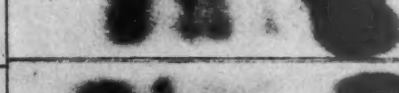
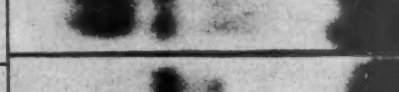

SUBJECT	ELECTROPHORETIC PATTERN	% $\gamma$ Glob.	F/M Ratio
Mother		15.4	0.40
Premature 6 months		6.2	
Mother		14.8	0.39
Premature 6 1/2 months		5.8	
Mother		13.6	0.68
Premature 7 months		9.3	
Mother		13.9	1.42
Full-term Newborn		19.8	
Newborn at birth		16.6	RATIO $\gamma$ GLOB. 65 D/BIRTH 0.19
Same, 65 days old		3.1	

Fig. 1. Evolution of the fetal/maternal gamma globulin ratio in function of the age of the fetus.

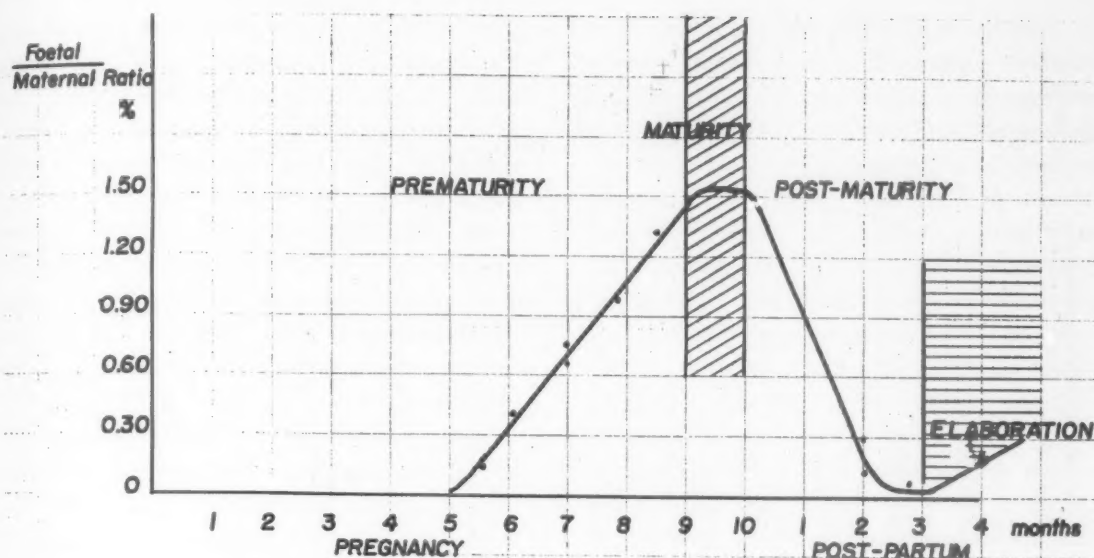


Fig. 2. Variation of the fetal/maternal ratio.

parameters in the samples taken at birth as well as during the first months of life. This is apparently in contradiction to our former findings regarding the  $\gamma$  globulin cycle; however, poliomyelitis antibodies are only a minute fraction of the entire  $\gamma$  globulin, and the only possible informative correlation would be between the sum of the known antibodies in the infant's serum and the level of the fetal  $\gamma$  globulin.

An interesting finding was the difference in the antibody titer in the serum of 2 non-identical twins (Fig. 3). This led to the following questions, the working hypothesis of the present paper: Is the placenta uniformly permeable for antibodies as well as for other constituents, as far as its entire area is concerned? In 2 separate placentas in one uterus (such as in the case of non-identical twins), would it be possible to detect physiological or even pathological differences in permeability by examining the comparative rates of transfer of antibodies or even of other metabolites?

The above points are examined in this paper; the placental permeability has been studied from both metabolic and immunological points of view. The level of naturally occurring poliomyelitis antibodies has been studied in the mother and in the newborn infant, simultaneously with a more detailed

analysis of the proteic components of the serum. The ratio between the transfer rate of antibodies and metabolites might offer information about the first question. The second point was approached by comparing the rate of transfer in twins, both identical and nonidentical.

#### Material and methods

The maternal and cord blood was taken from two groups of subjects: (1) six normal full-term single deliveries of either sex; (2) seven deliveries of twins (4 identical, 3 nonidentical) and one delivery of triplets. In one mother, labor was induced at term because of pre-eclamptic toxemia; another set of twins was 10 weeks premature; both survived and are well. The set of triplets was of approximately 5½ months' gestation, and they survived for a few hours after delivery; the onset of labor was spontaneous and its course uncomplicated. At the present moment all the babies except the triplets, their ages ranging between 6 and 9 months, are alive and well.

The blood samples were taken during parturition and a control sample was taken in the mother a few hours after delivery, in order to correct the possible errors due to changes in blood volume during delivery. The blood was collected and allowed to



clot, and the nonhemolyzed serum was immediately separated. The following determinations were carried out: (1) neutralizing poliomyelitis antibody titer, by the technique described in a previous paper<sup>5</sup>; (2) electrophoretic pattern and quantitative estimation of serum proteins by photometry and subsequent planimetry of the area; (3) lipoprotein electrophoresis with prestained serum and "cardboard separation."<sup>6</sup> The staining of the lipidic material prior to the electrophoretic run offers the advantage of leaving a white background on the paper, which is almost impossible to obtain in the classical procedure without a considerable loss of fats during removal of excess dyestuff. The quantitative estimate of lipoproteins was performed either by direct photometry and planimetry or by elution of the dyestuff and subsequent spectrophotometric determination at 680 m $\mu$ . Another sample of serum was simultaneously prestained with only 1/10 of the dyestuff and parallel mi-

gration of the lipoproteins was carried out; the cardboard was dried, cut into strips, and extracted with alcohol:ether (1:1). The total and esterified cholesterol was determined in each fraction; the presence of a small amount of dyestuff did not interfere with the Liebermann-Bouchard reaction, neither with its photometric determination. The cholesterol was determined by the Sperry-Schoenheimer method. In a few samples, simultaneous determination of the phospholipids was carried out in the lipidic extract of the separated fractions, by sulfo-perchloric digestion and subsequent phosphorus determinations by the Fiske-Subbarow procedure.

### Results

**A. Placental transfer of neutralizing poliomyelitis antibodies in twins.** The results are presented in Table I and Figs. 4 and 5. It has not been felt necessary to repeat the determination in control mothers, since this

Table I. Poliomyelitis neutralizing antibodies in parturient and twin serum

Subject	Type	Mother (average)	Twins (average)	Ratio F/M		Ratio Twin I/II	Remarks
Lal.	I	1/16	1/8	0.50		1.00	Identical
	II	1/258	1/65	0.25		0.63	
	III	1/102	1/50	0.50		1.00	
Sheil.	I	1/22	1/10	0.48		0.75	Identical
	II	1/8	1/5	0.60		1.00	
	III	1/26	1/8	0.31		1.00	
Kurtz	I	1/8	1/6	0.75		0.62	Identical
	II	1/5	1/5	1.00		1.00	
	III	1/22	1/22	1.00		0.36	
Amen.	I	1/10	1/4	0.40		1.00	Nonidentical
	II	1/32	1/32	1.00		1.00	
	III	1/300	1/850	2.82		2.40	
Smelt.	I	1/105	1/854	8.50		0.71	Nonidentical
	II	1/266	1/216	0.83		2.12	
	III	1/31	1/26	0.87		1.30	
Selc.	I	1/32	1/20	0.62		4.00	Nonidentical
	II	1/9	1/4	0.45		1.00	
	III	1/21	1/14	0.75		1.48	
Hers.	I	ø	ø	ø	ø	ø	Triplets
	II	1/14	1/15	1.07	1.28	0.40	
	III	1/400	1/12	0.03	0.72	1.45	
Sweet.	I	1/200	1/650	3.25		1.60	Pre-eclamptic toxemia
	II	1/410	1/220	0.54		2.20	
	III	1/10	1/15	1.50		2.75	

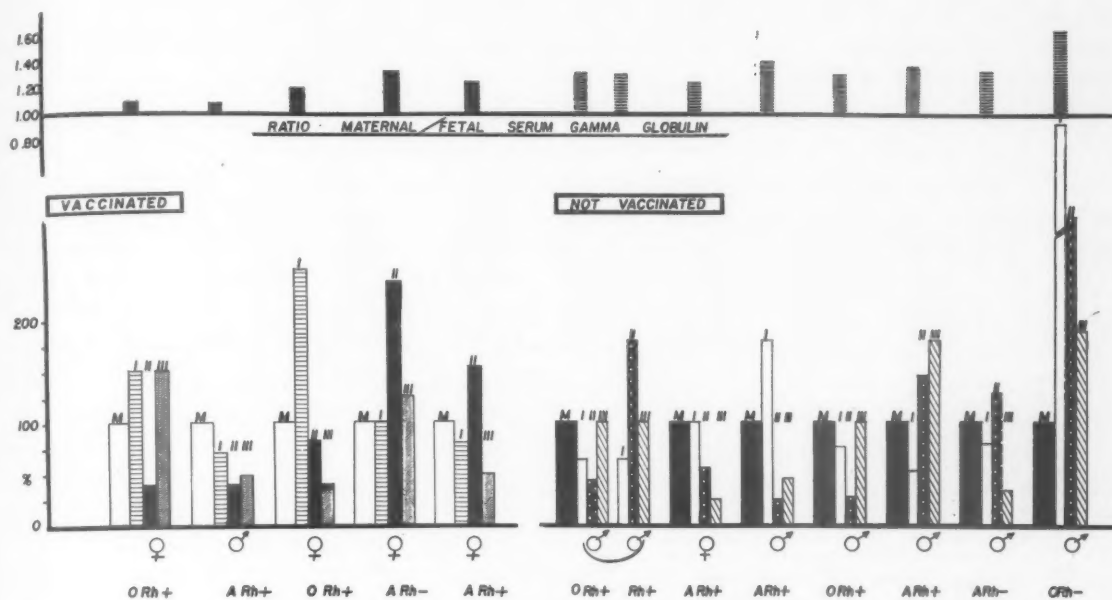


Fig. 3. Placental transfer of neutralizing poliomyelitis antibodies, relative values. M, maternal titer taken as 100 per cent; I, II, III, fetal titer for Types I, II, and III.

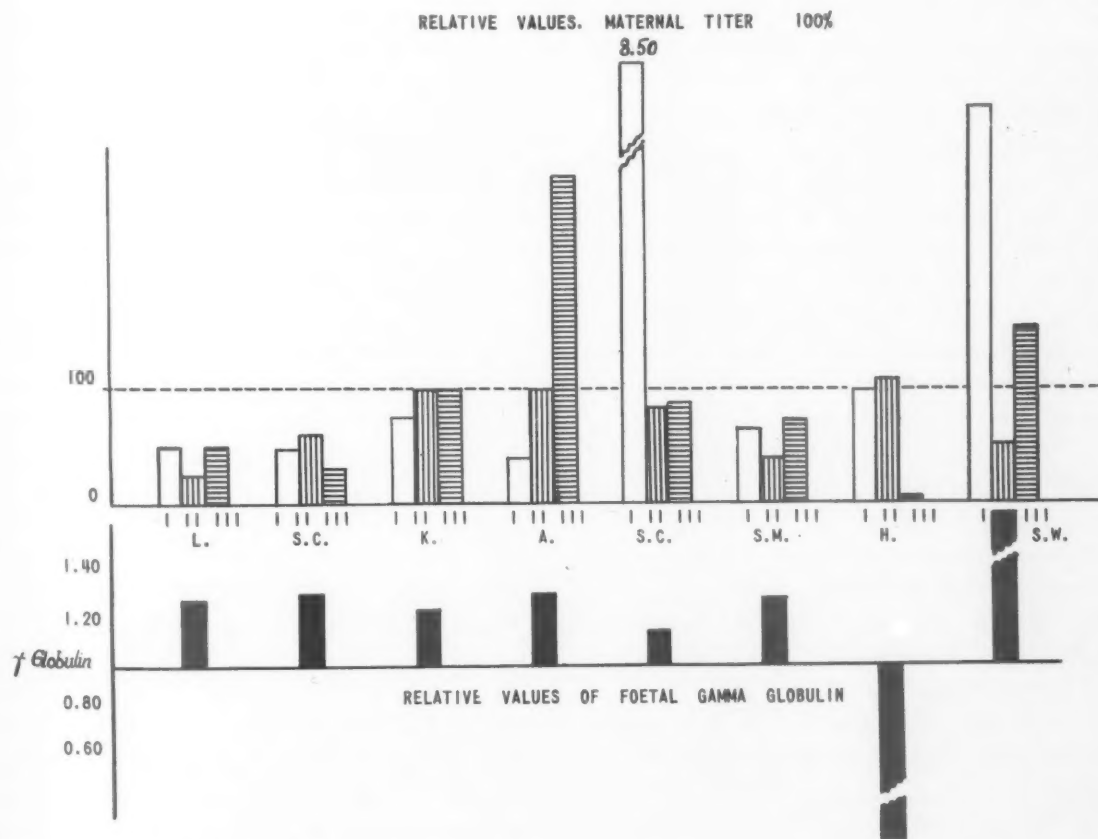


Fig. 4. Neutralizing poliomyelitis antibodies in twins.

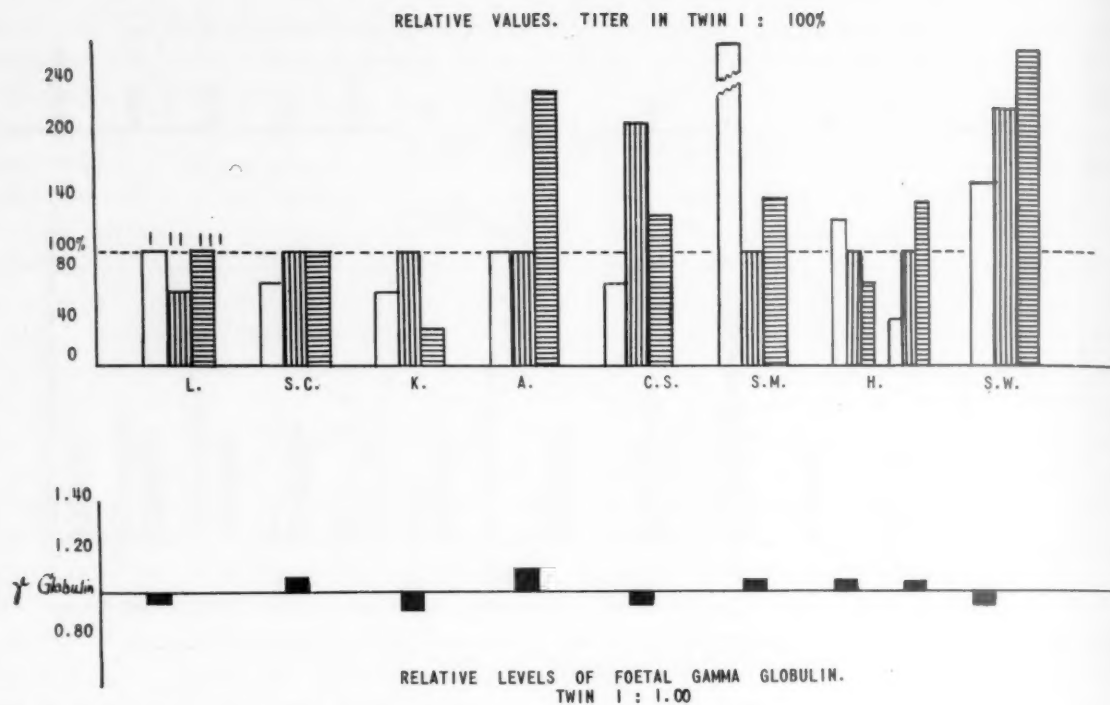


Fig. 5. Neutralizing poliomyelitis antibodies in twins.

has been established in our previous work. Several points should be noted on examination of the table and figures:

1. The placental rate of permeability of naturally occurring poliomyelitis antibodies in twins is not different from that of the control group of single deliveries. Also, the rate of transfer is similar to the rate noted in mothers who have been previously vaccinated with Salk vaccine.

2. The antibodies are transferred as early as the fifth month of gestation, as noted in the serum of triplets. It might be noteworthy to mention that even if the triplets did not survive because of atelectasis, they were already protected from the immunological point of view, at least with poliomyelitis antibodies.

3. The rate of antibody transfer is not influenced by the occurrence of pre-eclamptic toxemia.

4. The level of neutralizing antibodies in twins is in the same range and has the same wide variations as in single deliveries.

5. There is a significant similarity be-

tween the level of antibodies in the identical twins examined; the nonidentical twins did not exhibit this feature.

**B. Electrophoretic patterns of serum proteins in twins.** The electrophoretic patterns and the ratios fetal/maternal  $\gamma$  globulins are presented in Figs. 6, 7, and 8.

The following remarks must be made.

1. The previous assertion regarding the relative hypergammaglobulinemia in newborn infants is again confirmed in this work. Indeed, the full-term newborn infant had an average ratio fetal/maternal  $\gamma$  globulin of 1.35, with a range from 1.13 to 1.47 (the two patterns presented in Fig. 6). The two premature sets of infants, the twins and the triplets, exhibited a significant relative hypogammaglobulinemia, namely, 0.15 for the triplets (Fig. 7) and 0.68 for the twins. This last point is interesting, since the relatively significant amount of  $\gamma$  globulin in the serum of the 5½ months' triplets suggests that the  $\gamma$  globulin transfer has begun earlier than in the cases previously studied, where no  $\gamma$  globulin was detected at this stage.

2. In the serum of the case of pre-eclamptic toxemia, the ratio fetal/maternal  $\gamma$  globulin was significantly high—respectively, 1.63 and 1.54—but the mechanism of this phenomenon is different than that in normal deliveries. Indeed the maternal  $\gamma$  globulin is considerably diminished, while the fetal level is not affected in the same manner, having an absolute value near that of the serum of the other newborn infants. It might be speculated that although the toxemia alters the renal permeability for serum proteins, apparently it does not affect the placental permeability for  $\gamma$  globulins.

3. The electrophoretic pattern of serum proteins is remarkably similar in the twins as well as in the triplets, from the quantitative as well as the qualitative point of view. There is no significant difference between the electrophoretic pattern of the proteins of identical and nonidentical twins; how-

ever, there is a difference in the proteic pattern in the twins delivered of the toxemic mother; Twin I had a relatively higher  $\gamma$  globulin level and Twin II had a significantly higher  $\beta$  fraction (Fig. 8).

C. Lipoprotein patterns in twins. The results of the determination of lipoproteins are presented in Table II and Figs. 9, 10, and 11.

The lipidic material separated by our procedure has been designated by the following names: (1) neutral fats, (2) fatty acids, (3)  $\beta$  lipoprotein, and (4)  $\alpha$  lipoprotein. The first two fractions have been analyzed for their proteic content, and the absence of proteins entitled us to designate them as free fatty material. The neutral fat component is probably carried by the  $\beta$  lipoprotein during the electrophoretic migration constituting the well-known "trailing" process. However, there is another fraction

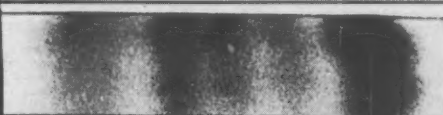
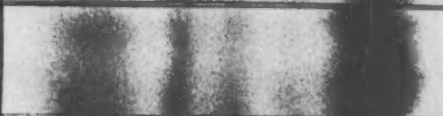
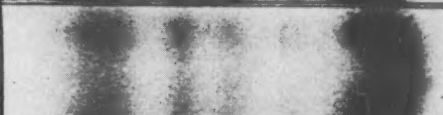
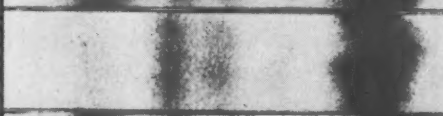
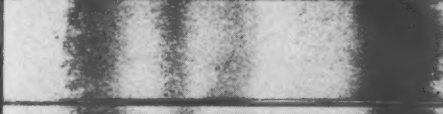

SUBJECT	PROTEIC PATTERN	T %	F/M	I/II
MOTHER		15.6 %	-	-
NON-IDENTICAL TWIN I.		17.4	1.13	0.98
TWIN II.		17.8	-	-
MOTHER		13.4	-	-
IDENTICAL TWIN I.		19.8	1.47	1.01
TWIN II.		19.6	-	-

Fig. 6. Proteic patterns in serum of full-term normal twins.



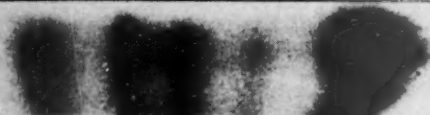
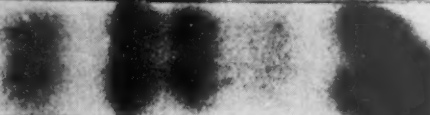



SUBJECT	PROTEIN PATTERN	%	F/M
MOTHER During Labour		15.3	
MOTHER After Delivery		15.6	
TRIPLET I.		6.9	0.45
TRIPLET II.		6.6	0.44
TRIPLET III.		6.7	0.44

Fig. 7. Electrophoretic patterns of serum proteins in serum of triplets (5½ months; survived 6 hours after delivery).

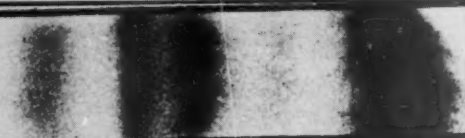
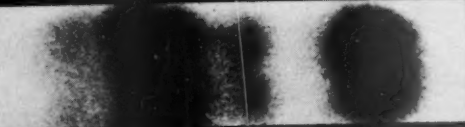
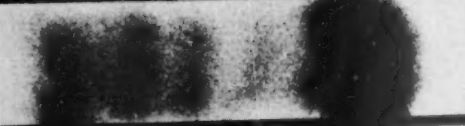
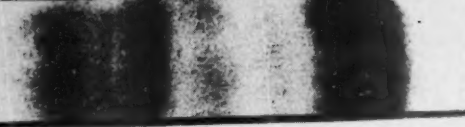
SUBJECT	PROTEIN PATTERN	%	F/M
NORMAL PREGNANCY		16.7	1.36
PRE-ECLAMPTIC TOXEMIA		11.5	
TWIN I.		18.7	1.62
TWIN II.		17.5	1.54

Fig. 8. Electrophoretic patterns of serum proteins in a case of pre-eclamptic toxemia.

**Table II.** Lipoproteins in maternal and cord serum (relative values: total lipoproteins = 100 per cent)

		NF	FA	$\beta$	$\alpha$	$\beta/\alpha$	$\frac{\beta + \alpha}{NF + FA}$
<b>Mothers</b>							
<b>Full-term normal deliveries</b>							
Single	Average ( 5)	40.4%	27.1%	35.4%	10.9%	3.40	0.93
	Range	31.9-54.0	18.4-36.0	22.8-43.5	7.4-15.7	2.70-4.60	0.43-1.41
Twins	Average ( 6)	37.4%	23.2%	34.4%	9.0%	3.85	0.86
	Range	31.8-48.5	9.0-30.1	20.1-48.2	3.2-14.0	2.1-7.1	0.34-1.45
<b>Pathological deliveries</b>							
<b>Premature (2)</b>							
Twins		32.1%	23.1%	37.3%	7.5%	5.05	0.81
Triplets		35.4%	19.6%	33.2%	11.8%	3.00	0.82
Pre-eclamptic toxemia (1)		25.7%	24.5%	35.8%	14.0%	2.50	1.00
<b>Newborn</b>							
Single	Average ( 5)	40.9%	31.0%	14.1%	11.0%	1.59	0.40
	Range	34.8-49.4	29.1-34.2	10.3-22.0	10.3-11.7	0.87-2.10	0.28-0.48
Twins	Average (12)	50.9%	30.0%	15.1%	8.5%	1.78	0.33
	Range	39.0-61.2	20.5-39.9	6.3-28.9	6.4-12.5	1.01-3.40	0.15-0.74
<b>Premature</b>							
	Average ( 5)	77.1%		13.6%	9.1%	1.50	0.29
	Range	71.0-82.6		10.5-16.8	6.9-12.2	1.3 -1.61	0.21-0.35
I		41.0%	35.7%	19.8%	3.5%	5.7	0.32
Pre-eclamptic toxemia (one set of twins) II		47.9%	33.4%	13.8%	4.9%	2.8	0.23

which migrates through the electrophoretic field despite its lack of proteins. Its speed is considerably slower than that of the lipoproteins. We have designated this fraction "fatty acids" without having the analytical proof that it is constituted by fatty acids, the only fatty material whose small electrical charge allows a reduced degree of migration. The fatty acids do not appear consistently in the lipidogram; often they remain in the neutral fat fraction. We have established a ratio expressed by the formula  $\beta + \alpha / NF + FA$  and indicating the amount of lipids incorporated in the lipoproteins as related to the total lipidic content of the serum.

The  $\beta$  and  $\alpha$  lipoproteins do not differ in our procedure from the fractions obtained by the classical electrophoretic separation with thin paper and poststained serum. However, a salient feature of the cardboard electrophoresis with prestained serum is the visible difference between the lipidic

material, stained deep blue by the acetylated Sudan Black NB, and the hemoglobin or bilirubin (Fig. 9). Hemoglobin migrates before the  $\beta$  lipoprotein as a reddish-brown stained zone, while bilirubin migrates usually with the albumin fraction (probably the direct fraction in the Van der Bergh reaction) constituting a faint orange zone detectable especially in the newborn infant's serum. Often it is possible to note a brownish zone near the  $\beta$  lipoprotein, markedly visible in the serum in pathological deliveries (Fig. 11); the nature of this pigment has not been determined as yet.

The presence of the various zones distinctly colored is an advantage for direct examination of the lipoproteic pattern, inasmuch as it allows immediate detection of hemolysis or bilirubinemia. On the other hand, it is an obstacle for direct photometric estimation as the values of light transmission are too high in the pigmented zones and give erroneous results in the direct es-



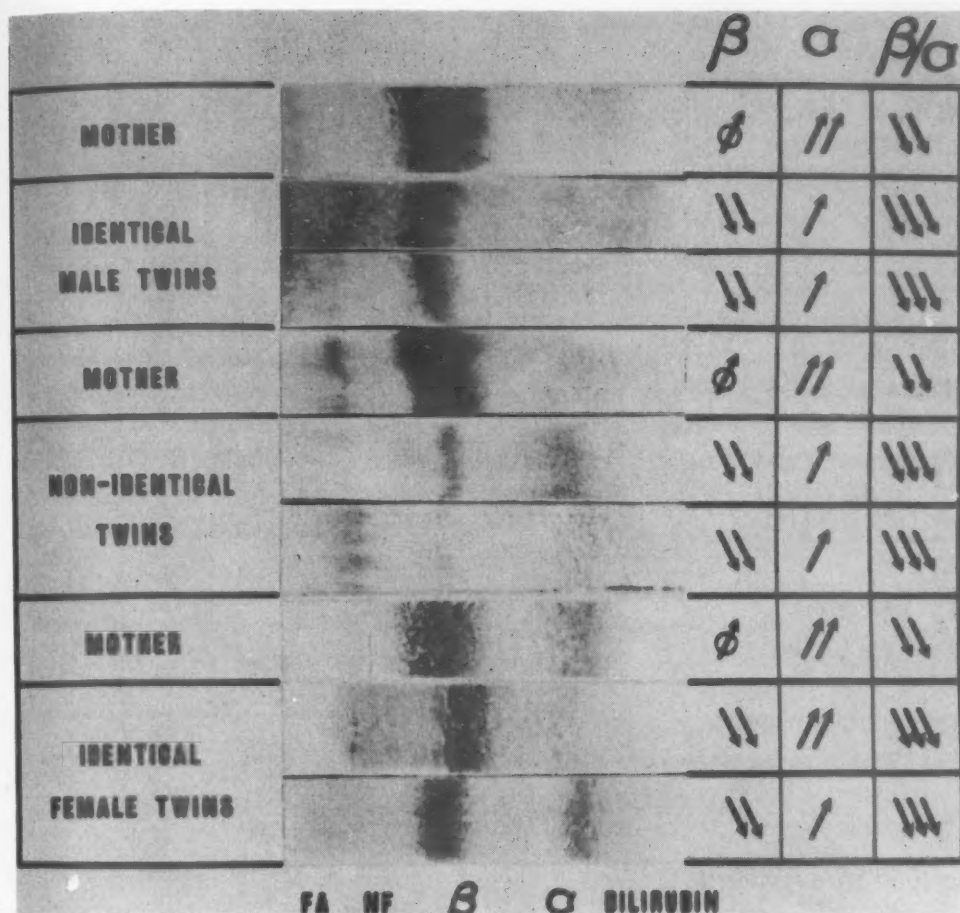


Fig. 10. Lipoprotein patterns in serum of mothers and twins.

Therefore, if the  $\beta/\alpha$  ratio does not diminish significantly during pregnancy, then the mechanism of the "lipodiatic action" plus that of estrogen must be related to other factors.

2. The lipoprotein pattern in serum of parturient women is not significantly different from that of the pattern during pregnancy; the ratio  $\beta/\alpha = 3.40$  is well in the range of pregnant and nonpregnant women. There is no significant difference in the lipidogram of women delivered of single babies or twins.

3. The lipidogram of the full-term normal newborn infant is characterized by the following features:

a. A significant relative decrease of the ratio  $\beta + \alpha/NF + FA$ , which reaches values ranging between 0.20 and 0.70, with an

average of 0.40. This is less than half the value in mothers, suggesting that the newborn infant uses more free fats than lipoproteins, in opposition to the adults, who use more lipoproteins than free fats.

b. A significant relative decrease of the  $\beta$  lipoprotein, which diminishes from an average of 33 to 37 per cent in the mother to 13 to 15 per cent in the newborn infant.

c. On the other hand, there is an increase of the  $\alpha$  lipoprotein, whose absolute value is 11.0 per cent in single deliveries.

d. Obviously, the ratio  $\beta/\alpha$  is considerably lower than in maternal serum, owing to the two changes previously mentioned. The ratio  $\beta/\alpha$  averages 1.59 in newborn, as compared to 3.40 in parturient serum.

e. The lipoproteins of the twins are similar to those of single deliveries, in so far as



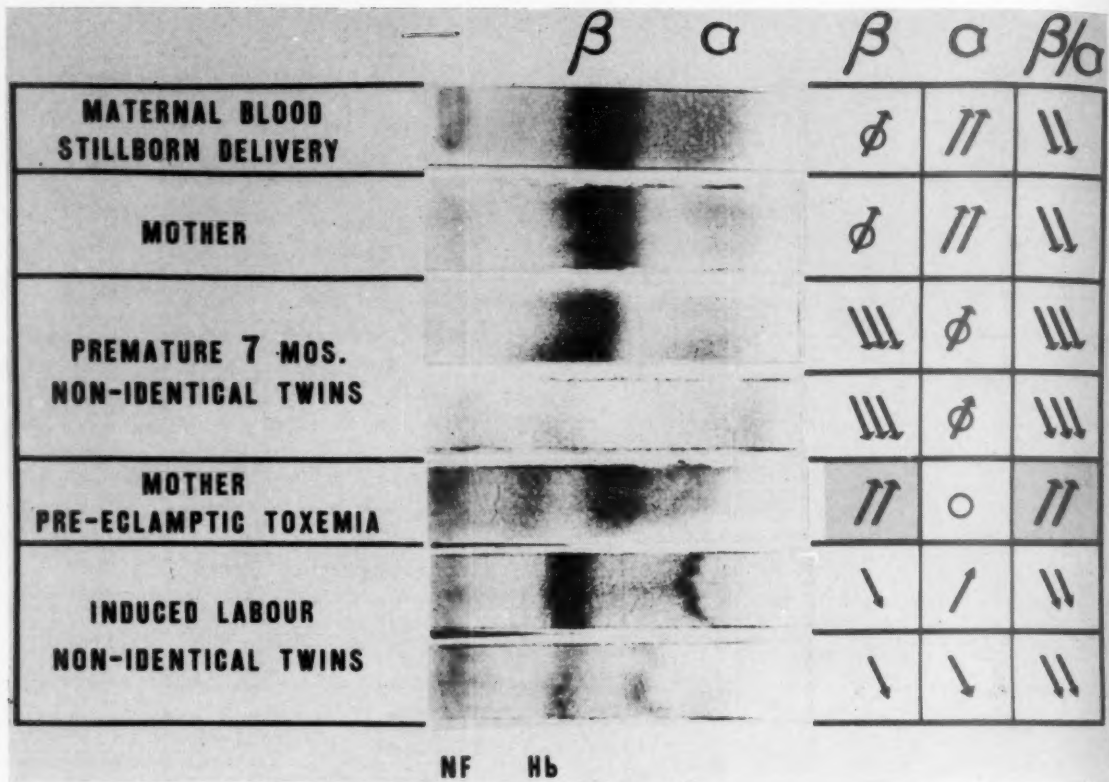


Fig. 11. Lipoproteins in serum of mothers and twins in premature or toxic deliveries.

the former features are concerned. The  $\beta/\alpha$  ratio is 1.78 (1.01-3.40) and the  $\beta + \alpha/\text{NF} + \text{FA}$  averages 0.33 (0.15-0.74). There are no significant differences between the lipoproteins of identical and nonidentical twins.

f. The sex factor is of no importance inasmuch as the lipoprotein pattern is concerned; the female single and twin newborn infants have the same amount of  $\alpha$  lipoproteins as the males. Of course, one has to take into account the high level of circulating estrogens in the blood of the newborn of either sex, a fact which might be related to the relatively high level.

g. The premature twins or triplets do not differ in their lipidogram from the full-term twins; perhaps the ratio  $\beta + \alpha/\text{NF} + \text{FA}$  is lower, ranging between 0.21 and 0.35, with an average of 0.29; the  $\beta/\alpha$  ratio has the same values as in the other newborn infants, averaging 1.50 (1.30-161).

h. The twins delivered of the toxemic mother have a lipidogram with the same

low  $\beta$  fraction as in the other cases, but in one case the level is 19.38 per cent, whereas the second twin had only 13.8 per cent. The  $\alpha$  lipoprotein was significantly lower than in normal deliveries, respectively, 5.7 per cent and 2.8 per cent instead of 9 to 11 per cent as in the normal newborn infants. Naturally, the  $\beta/\alpha$  ratio is higher than the average, 5.7 and 2.8, respectively, while the  $\beta + \alpha/\text{NF} + \text{FA}$  ratio shows less accentuated variation (0.23 and 0.32). It is important to note that only in twins of toxemic mother have we found a difference between the 2 newborn infants, in the proteic pattern as well as in the lipidogram (Fig. 12).

D. Cholesterol determination in the lipoprotein fractions. The total cholesterol level in the serum of pregnant women of this investigation ranges between 160 mg. per cent and 405 mg. per cent, with an average of 245 mg. per cent. There is no significant difference in the cholesterol value in the serum of parturient women with single de-

liveries or twins, either at full-term or at premature delivery. Also, the serum of the mother of triplets did not deviate from the average range. The patient with pre-eclamptic toxemia had a high value—410 mg. per cent—but this value does not seem sufficiently high to justify it as a special feature.

The analysis of the distribution of cholesterol in the lipoproteic fractions leads to the following conclusions:

1. The neutral fat and fatty acid fractions are devoid of cholesterol; the traces which are usually detected are probably due to trailing of the  $\beta$  lipoprotein cholesterol. This is true in mothers as well as in newborn infants.

2. The  $\beta$  fraction contains the largest amount of cholesterol, ranging between 115 and 294 mg. per cent, with an average of 165 mg. per cent; the  $\alpha$  fraction has far less cholesterol, averaging 35 mg. per cent. If the respective ratios of the lipoproteins are compared to their cholesterol content, one might assume that the cholesterol is evenly distributed in the lipidic material of each lipoprotein. The ratio of  $\beta/\alpha$  cholesterol

reflects the  $\beta/\alpha$  lipoprotein findings; its values average 4.0 (1.7-6.7). The ratio of esterified/free cholesterol, presented here in only a few cases, did not exceed the normal range (0.3).

3. The cholesterol content of the cord blood is considerably lower than that of the corresponding maternal blood. The average value is 110.0 mg. per cent with a range of 57.2-130.8 mg. per cent. There is no significant difference between the cholesterol level in single or twin deliveries, nor did the serum of premature twins show any difference from the average value (109 and 110 mg. per cent). The highest value noted was in one of the twins delivered of the toxemic mother (139.8 mg. per cent). It is unfortunate that the amount of serum of the triplets was not sufficient to afford an accurate evaluation of the cholesterol level.

4. The distribution of the cholesterol in the lipoproteic fractions leads to the interesting constataion that the fetal  $\beta$  lipoprotein contains significantly less cholesterol than the same fraction in the maternal blood; the  $\beta$  fraction has a cholesterol level ranging between 33.1 and 73.8 mg. per

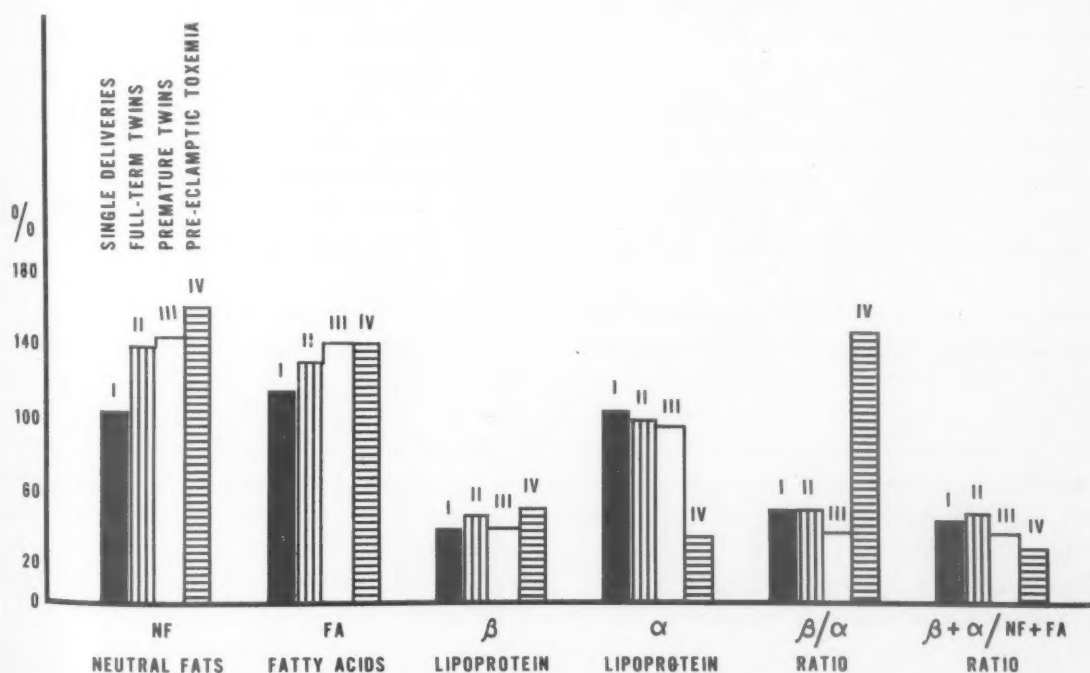


Fig. 12. Comparison between the lipoprotein level in fetal and maternal blood, relative values. Maternal level, 100.

Table III. Cholesterol level in serum lipoproteins in parturient and newborn

Subject	Total cholesterol (mg.%)	$\beta$ lipoprotein (mg.%)	$\alpha$ lipoprotein (mg.%)	Ratio $\beta/\alpha$
Single deliveries				
Maternal serum	263 (172-363)*	203 (109-246)	80 (48-118)	2.54 (1.71-4.40)
Cord serum	118 (101-133)	61 (52-74)	57 (44-69)	1.07 (0.89-1.24)
Ratio fetus/mother	0.42 (0.32-0.77)	0.30 (0.21-0.68)	0.71 (0.61-0.94)	0.42 (0.31-0.54)
Twin deliveries				
Maternal serum	248 (173-300)	206 (130-294)	33 (28-43)	6.24 (3.00-7.43)
Cord serum	92 (57-124)	51 (33-69)	41 (19-56)	1.24 (0.73-1.98)
Ratio fetus/mother	0.37 (0.23-0.72)	0.25 (0.18-0.53)	1.24 (0.69-1.53)	5.00 (3.21-6.65)
Premature twins				
Maternal serum	264	199	65	3.06
Twin I	110	67	43	1.55
Twin II	109	62	47	1.32
Ratio fetus/mother	0.42	0.32	0.69	0.52
Pre-eclamptic toxemia				
Maternal serum	406	282	124	2.25
Twin I	140	109	31	3.51
Twin II	120	87	33	2.64
Ratio fetus/mother	0.32	0.35	0.26	1.17-1.51

\*Range is in parentheses.

cent, while the  $\alpha$  fraction averages almost the same value. The  $\beta/\alpha$  ratio is significantly lower in newborn infants, sometimes being even less than 1.0.

This constataion is valid for single deliveries as well as for twins or premature deliveries. The sole exception is constituted by the serum of the twins delivered of the toxemic mother, where the  $\beta/\alpha$  cholesterol ratios have the respective values 3.51 and 2.64.

The cholesterol level in twins does not show significant differences beyond the analytical error of the determination; this is valid in identical or nonidentical twins. The greatest difference between twins has been noted in the toxemic case, where the values were, respectively, 139.8 mg. per cent and 120.0 mg. per cent.

5. Comparison between the cholesterol in the maternal and newborn lipoproteic fractions gives the following data:

Fetal  $\beta$  lipoproteic cholesterol/maternal  $\beta$  lipoproteic cholesterol = 0.27 (0.18-0.67).

Fetal  $\alpha$  lipoproteic cholesterol/maternal  $\alpha$  lipoproteic cholesterol = 1.18 (0.59-1.54).

There is no difference between twin and single deliveries, nor between premature and full-term newborn infants. Only the  $\alpha$  fetal/maternal ratio in the toxemic patient is considerably lower (0.33) instead of the average 1.18 value, while the  $\beta$  fetal/maternal ratio does not differ significantly from the average (0.26 versus 0.27).

#### Comment

The salient features of this investigation have been discussed during the presentation of the results, therefore, we will now endeavor to answer the 2 working hypotheses mentioned at the beginning of the paper.

1. Does the placenta have uniform permeability for the various constituents examined (antibodies, proteins, lipoproteins, cholesterol)?

The answer to this question is offered by the examination of the ratio of fetal/maternal level in the various constituents stud-

ied. A first constatation is the well-established finding of the relative hypergamma-globulinemia in newborn infants, as well as the relative hypogammaglobulinemia in the premature infants. Fig. 13 summarizes the observations of this investigation:

If we take into account only this ratio, we must overlook the important factor of the cord blood level of the constituents elaborated by the fetus. This could considerably modify some data, but the general aspect of the phenomenon can be inferred safely from this schema, even if the level of the fetal metabolites is unknown at present.

Nevertheless, it should be said that the  $\gamma$  globulins as well as their carried antibodies are exclusively elaborated by the mother, so that the fetal level represents only the transfer rate; as for the other constituents of fetal origin, our present techniques are unable to discriminate between a maternally elaborated and a fetally elaborated metabolite. Perhaps new immunochemical or radioisotopic approaches will shed some light upon this point, as they succeeded in identifying fetal hemoglobin by paper electrophoresis.

With this restriction, the examination of

Fig. 13 shows that the constituents in equilibrium are:  $\alpha_1$  globulins,  $\alpha$  lipoproteins, and poliomyelitis antibodies. The placental permeability is definitely *increased* in the case of  $\gamma$  globulin and free fats, and we can speak of *decreased* permeability in the case of  $\beta$  and  $\alpha_2$  globulins,  $\beta$  lipoproteins, and cholesterol. In the last case the decrease must be considered as real, for it is established that the fetus elaborates cholesterol; thus, the actual decrease must be lower even than the calculated one. As for the free fats, the increased placental permeability should be accepted only as an alternate hypothesis to that of a modified integration rate of the free fats in the fetal lipoprotein molecule as compared to the maternal integration rate.

There is no relationship between molecular weight or size of the transferred constituent and its rate of permeability; thus, the permeability is increased for free fats (M.W. = 800) as well as for the  $\gamma$  globulin (M.W. = 150,000-300,000), whereas the permeability is decreased for the small sized cholesterol molecule (M.W. = 370) as well as for the huge  $\beta$  lipoprotein (M.W. = 1,300,000-3,000,000). Of course, one must consider that cholesterol is still an integral

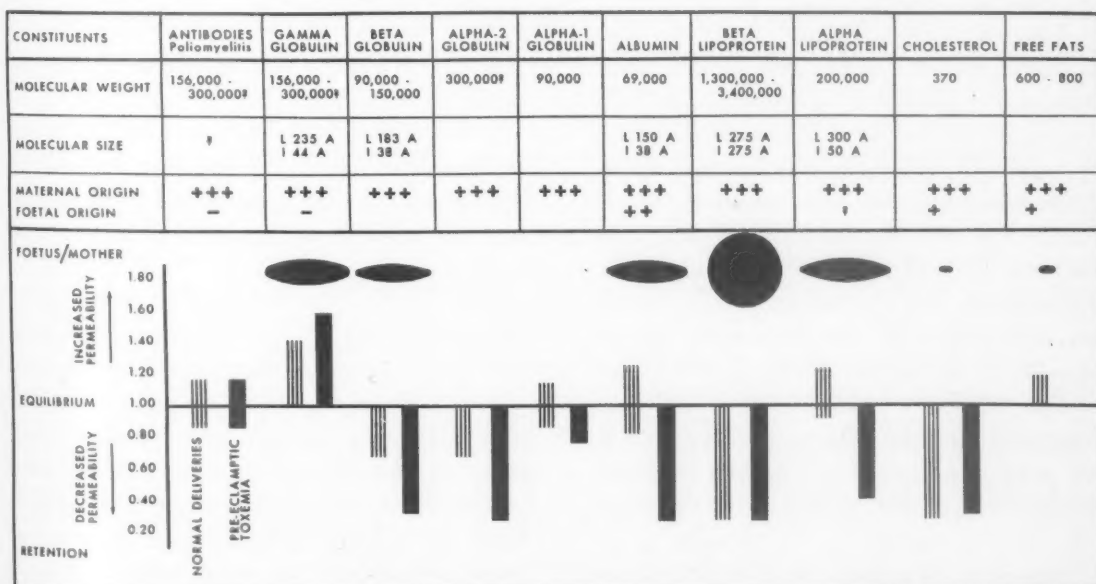


Fig. 13. Comparative study of fetal/maternal ratio of serum constituents as related to their molecular size and shape.



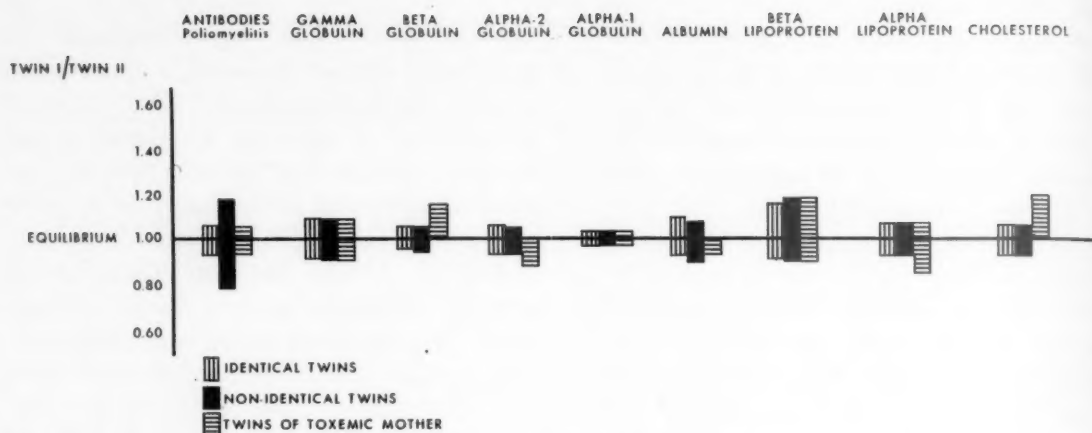


Fig. 14. Comparison between the concentration of antibodies and metabolites in serum of identical and nonidentical twins.

part of the lipoproteins during the transfer, but the data found in the literature confirm this random rate of transfer for other metabolites.<sup>7-10</sup>

Could one speculate that the mechanism of placental transfer is not merely a passive physicochemical selective filtration process, but that it involves a more active secretion process localized in the placental tissue? The problem is far from being understood at present, but experiments with  $P^{32}$  made as early as 1942 by Nielson<sup>11</sup> suggest that there might be a breakdown of the phospholipidic molecule in the placenta, with a further resynthesis in the fetal blood; this has been reinvestigated later by Popjak with similar conclusions.<sup>12</sup> The slow transfer of liposoluble vitamins A and K have suggested to Lund and Kimble<sup>13</sup> that they might be retained by placental lipids.

In summarizing, the data obtained in this investigation are in concordance with the abundant material found in this subject in the literature, but the interpretation varies from other opinions<sup>3</sup> attributing an important role in the permeability to molecular size; this has been found to be in the case of autoantibodies by Wiener and Sonn,<sup>3</sup> but more work is necessary in order to establish a relationship between these two parameters.

It must also be emphasized that the study of the maternal and cord blood does not represent the true rate of transfer occur-

ring during pregnancy, since the maximum rate of transfer has been established by investigators to be in the decline preceding the parturition.

2. Is the rate of transfer similar in two regions of the same placenta, or in two separate placentas in one uterus?

The answer to the first part of this question is very difficult to give for human placentas, although it might be speculated that a large single placenta could have areas of varying rates of transfer. In our opinion however, this is not the core of the problem, because investigations with labeled substances have shown that the turnover rate of the transferred substance is the essential feature in maternal-fetal exchanges.<sup>14, 15</sup>

The second part of this question could be summarized in the graphic representation of the rate of transfer in twins, by taking the relative values of their transferred constituents.

The examination of Fig. 14 leads to the conclusion that the metabolites have almost the same values in twins, be they identical or nonidentical, full-term or premature. The only difference between the twins has been noted in neutralizing antibodies, which have similar levels in identical twins and variable levels in nonidentical twins. However, one must be cautious in taking this fact as a sign of variability in the rate of transfer in two separate placentas, for the antibody de-

termination is subject to a higher degree of fluctuation than the chemical assay of metabolites.

The comparison between the metabolites of twins in pre-eclamptic toxemia shows that there are significant variations in some constituents, such as the  $\alpha_2$  globulins, the  $\alpha$  lipoproteins, and cholesterol. It is interesting to note that the newborn infants were of different sizes, a fact which might be in accordance with the variation found in the serum constituents.

For the time being, we must conclude that in normal pregnancies the placenta has the same rate of permeability throughout its entire area. The pathological placenta, such as in pre-eclamptic toxemia, has probably regions of variable permeability.

This assumption opens the way to investigations in the placental permeability in pathological pregnancies, and it might lead to findings useful for the diagnosis of metabolic disturbances during pregnancy.

### Conclusions

1. The rate of transfer of poliomyelitis antibodies in twins is similar to that previously found in single deliveries; it is not changed in premature twins, neither in twins delivered by a toxemic mother. The antibody titer in nonidentical twins is more variable than in identical twins. There is no significant relationship between the  $\gamma$  globulin level and the antibody titer.

2. The  $\gamma$  globulin level in twins averages the same higher relative value than the maternal level in full-term deliveries; it is lower than the maternal level in premature twins or triplets. There is significant similarity between the proteic compounds of the twin's serum, either identical or nonidentical.

3. The lipidogram of the newborn is characterized by a high neutral fat and fatty acid content and a significantly low  $\beta$  fraction and  $\beta/\alpha$  ratio. The  $\alpha$  lipoprotein has almost the same absolute values in the mother as in the newborn infant. There is no significant difference between the lipidogram in twins, be they full-term or premature, identical or nonidentical.

4. The cholesterol level in newborn infants is closely related to the lipidogram. There is a significant diminution of the cholesterol content of the  $\beta$  lipoprotein in newborn, as compared to the maternal values; no significant differences have been noted between the cholesterol levels in the serum of each of a set of twins.

5. There is no uniform permeability for the examined constituents; no relationship has been found between the rate of transfer and the molecular size or molecular weight of the transferred constituents.

6. In normal pregnancies, the placenta has apparently the same permeability throughout its entire area, as noted in identical and nonidentical twins. This was not found in a case of pre-eclamptic toxemia.

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# The significance of placental/fetal weight ratios

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THE small "insufficient" placenta has been a speculative issue for some time. Interest in this subject was provoked by the recent birth at the Sloane Hospital for Women of a 3,500 gram term infant with severe acidosis (pH 6.87) and markedly deranged metabolism without apparent etiology except the presence of a placenta of 187 grams (placental coefficient 0.053). The literature contains a paucity of controlled and definitive data for standardization or interpretation of the significance of placental/fetal weight ratios.

In 1925 Adair and Thelander<sup>1</sup> summarized the literature and noted that most authors had observed that placental weight varied with fetal weight, but otherwise noted no correlations. Subsequent studies, in general, were concerned with only the weight of the fetus<sup>12</sup> or with the relationship of fetal weight and placental weight.<sup>3</sup> In one instance,<sup>4</sup> an intensive mathematical study was made of the relationship among placental weights, placental areas, gestational sac sizes, and fetal weights.

In a study of birth weights and placental weights in pre-eclampsia, Baird and associates,<sup>2</sup> in contraposition to previously published opinions,<sup>1,6</sup> concluded that the "small baby syndrome" was a rarity. Schömig<sup>8</sup> scrutinized placental anomalies in regard to fetal weight and noted the adherent placenta to be slightly smaller than other placentas.

Schaeffer, as noted by Needham,<sup>7</sup> described in 1898 a decrease in the placental/fetal weight ratio as gestation progressed. Although few contributors have studied this ratio in respect to gestation, a summation

of the data recorded in the literature,<sup>5, 7, 11</sup> determination of the mean placental/fetal weight ratios from this data, and the plotting of these mean values versus the length of gestation result in a hyperbolic curve (Fig. 1). During the first weeks of gestation the trophoblastic tissue weighs more than the fetus as evidenced by a ratio greater than one. The ratio reaches equivalence at about 3½ months' gestation and thereafter shows a gradual decline. At term the placenta weighs about one seventh as much as the infant.

Sinclair,<sup>9</sup> in 1948, utilizing standardized methods, plotted placental/fetal weight ratios versus the weight of the infant. He estimated a probable absolute minimum ratio (0.10 to 0.11) which would be compatible with intrauterine life. In a subsequent publication,<sup>10</sup> however, he noted a live birth in which the ratio was 0.064. No description of the case was given. He concluded from his data that the human placenta undergoes changes during gestation which increase its capacity to transfer metabolites and compensate for its slow growth when compared to the fetus. Relative immaturity in the placenta corresponded to a high placental/fetal weight ratio and relative maturity to a low ratio. Sinclair<sup>10</sup> observed that with a high placental/fetal ratio the infants were frequently lethargic or suffered from hydrops fetalis of Rh incompatibility or were reactors to maternal diabetes or hypothyroidism.

In 1954, Kloosterman and Huidekoper<sup>3</sup> studied placental/fetal weight ratios (placental coefficients) in term and postterm births. Their 731 infants born at term with normal placentas had a mean ratio of 0.148 while those born postterm (after 290 days) had a mean ratio of 0.144. From their observations, a placental coefficient less than

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0.13 in the presence of placental infarction and a placental weight of less than 500 grams was associated with an intrauterine death rate of 17 per cent. The disparity between the above authors' ratios is apparent.

### Methods

The placental/fetal weight ratios, hereafter termed as placental coefficients, were determined in 956 consecutive third trimester deliveries. The only selection of cases was that the length of gestation be greater than 28 weeks and that the last menstrual period be ascertained with some degree of confidence.

In order to avoid errors in mensuration, all placentas were prepared in a similar manner. The cord was excised 5 cm. from the chorionic plate, the extraneous membranes were trimmed close to the placental margin, four 2 to 3 cm. incisions were made through the large vessels in the chorionic plate in order to provide adequate drainage of excess blood, the placentas were cleansed free of excess blood and clots, and all the placentas were weighed with the same scale. The length of gestation was calculated by the method of Naegele. The placental coefficient was ascertained by dividing the placental weight in grams by the fetal weight in grams. In multiple gestations in association with a single placenta, the placental coefficient was calculated by using the sum of the fetal weights as the denominator.

### Results

The mean gestational age for the 956 cases is 38.8 weeks, which is comparable to the data of others.<sup>5, 11</sup> The fetal weights, placental weights, and placental coefficients are expressed as the mean  $\pm$  1 standard deviation\* in Table I by 2 week increments. The period of 37 to 41 weeks' gestation is colligated as a term group and 42 weeks'

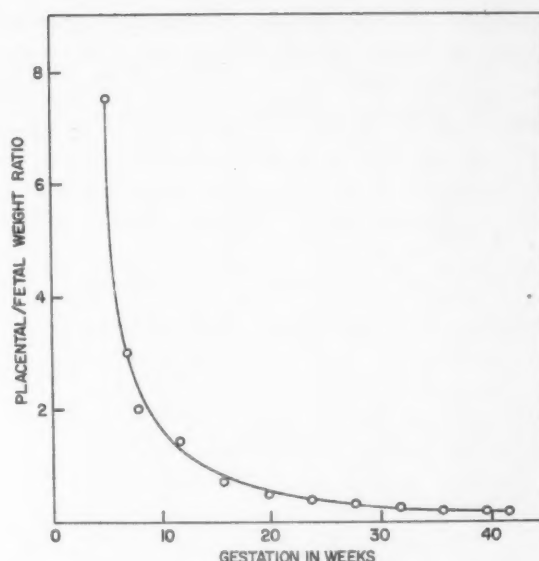


Fig. 1. Placental/fetal weight ratios versus length of gestation as determined from values in the literature.

gestation as a postterm group. As the third trimester progresses, the placental coefficient gradually decreases while the fetal and placental weights gradually increase. The placental coefficient is essentially stable after 37 weeks' gestation. The rather large standard deviations in the early weeks of the third trimester occur by dint of small population samples. The rather large standard deviations in the placental and fetal weight groups attest to the wide weight variations that are present at any stage of gestation.

If one considers the 837 cases with 37 or more weeks of gestation, in regard to the normal frequency of distribution, one may anticipate that approximately 95 per cent of placentas will have a placental coefficient between 0.10 and 0.18. One may further expect that only one of every 300 cases would have a placental coefficient less than 0.08 or greater than 0.20. Therefore, any term birth which has a placental coefficient less than 0.10 may be considered as a relatively small placenta and less than 0.08 may be assuredly termed an abnormally small placenta. A relatively large term placenta may be defined as having a placenta coefficient greater than 0.18. An abnormally

\*Standard deviation (s.d.) =  $\sqrt{\frac{\sum d^2}{n}}$  where d = deviation from the mean and n = number of observations.



Table I. Third trimester fetal weights, placental weights, and placental coefficients

Weeks of gestation	No. of cases	Placental weight	Fetal weight	Placental coefficient
28-30	8	344 ± 80*	2,108 ± 1,055	.193 ± .074
31-32	19	403 ± 153	2,330 ± 940	.187 ± .072
33-34	36	395 ± 77	2,642 ± 581	.152 ± .028
35-36	56	413 ± 92	2,800 ± 618	.147 ± .029
37-41	750	451 ± 89	3,215 ± 493	.140 ± .022
42+	87	482 ± 95	3,410 ± 52 <sup>^</sup>	.141 ± .021
Total	956	448 ± 93	3,169 ± 547	.142 ± .028

\*All values expressed as mean ± 1 standard deviation.

large term placenta may be identified by a placental coefficient greater than 0.20.

Further evaluation of these 837 cases reveals 11 cases with placental coefficients less than 0.1 and 13 cases with coefficients greater than 0.18. The mean weight values for these placentas (Table II) demonstrate that the high coefficient cases are associated with placentas weighing almost twice as much as the low coefficient cases while the mean fetal weight in the high coefficient group is only 1/10 less than in the low coefficient cases. Therefore, the major variation is in placental weights.

These 24 cases did not vary significantly from the remaining 813 cases in respect to maternal age, parity, or hypertension. There was no instance of toxemia or other significant maternal derangement except one case of polyhydramnios of unknown etiology. This case was associated with a high coefficient value. Contrary to expectations, there were no diabetic, syphilitic, or erythroblastotic placentas in the high coefficient group.

In spite of the small number of cases,

there is an apparent increase in the incidence of circumvallate and severe circummarginate placentas: 2 circumvallate placentas in the low coefficient group and 2 severe circummarginate placentas in the high coefficient group. There were 4 cases of fetal distress,\* 2 in each group. One stillbirth of unknown etiology, in which necropsy revealed only evidences of anoxia, was associated with a placental coefficient less than 0.10. If one is permitted to embellish one's data by considering those cases where the placental coefficients are less than 0.10 and greater than 0.18 as one group, these cases may be compared with the 813 cases falling within the mean ± 2 standard deviations (Table III). The probabilities of chance occurrence of the severe circummarginate and circumvallate placentas, unexplained stillbirth, and fetal distress cases are < .02, < .001, and < .01, respectively. The chi-square test,† utilized for these determinations, is somewhat unreliable when applied to small numbers of cases. This modifies the validity of these apparently significant differences.

Comment

It would seem that the case cited in the introductory remarks where the placental coefficient was 0.053 (more than 4 standard deviations from the mean) is associated

Table II. Weight values in deviates exceeding the mean ± 2 standard deviation (37± weeks of gestation)

	Placental coefficient > .180	Placental coefficient < .100
Number (n)	13	11
Placental weight (mean)	587 grams	323 grams
Fetal weight (mean)	3,045 grams	3,344 grams

\*Fetal distress is defined as persistent slowing of the fetal heart tones to less than 100 beats per minute between uterine contractions.

†Chi-square test:  $\chi^2 = \sum \frac{(f-f_1)^2}{f_1}$  where f is the observed frequency of occurrence and f<sub>1</sub> is the frequency expected according to a hypothesis.

**Table III.** Frequency of complications in deviate versus normal placentas (37+ weeks of gestation)

	Cases within mean $\pm$ 2 S.D.	Cases outside mean $\pm$ 2 S.D.
Number (n)	813	24
Fetal distress	24 (3%)	4 (16.5%)
Stillbirths, unexplained	5 (0.6%)	1 (4.2%)
Circumvallate or severe circummarginate placenta	40 (4.9%)	4 (16.7%)

with an extraordinarily small placenta. The exhibited abnormal metabolism might conceivably be secondary to "placental insufficiency" or a lack of placental reserve. The former phrase is used with reticence because it has been recently overused for any unexplained fetal-placental mishap or variation.

The purpose of this presentation is to determine the normal frequency distribution of the placental coefficient and to define the small and the large placenta. If one makes the assumption that the standard deviation of the mean of the placental coefficients is approximately the same at any stage of the third trimester as it is at term, one may calculate the probable limits of normalcy for earlier stages of gestation by referring to the means expressed in Table I. For example, any placental coefficient less than 0.09 or greater than 0.21 might be considered abnormal at 32 to 34 weeks of gestation. Any coefficient less than 0.13 and greater than 0.25 might be considered abnormal at 28 to 30 weeks of gestation. Of course, such calculations are only approximations.

The apparently increased frequency of stillbirth and fetal distress is provocative. The validity of these observations may be questioned because of the limited number of cases. The presence of 2 circumvallate placentas in association with small placental coefficients fits the predicted.

To consider the placental coefficient, per se, as a measure of placental sufficiency or

reserve would be a naïve view. Undoubtedly, pathological changes, variations at the cellular level, and numerous other factors will modulate the significance of the placental coefficient in a given case. One has only to view Fig. 1 to be impressed by the adaptability of the placental-fetal relationship.

### Summary

The placental coefficient (placental weight/fetal weight) was determined in 956 third trimester births in order to ascertain and define the abnormally small or large placenta. With the described methods, any term infant with a placental coefficient less than 0.10 and greater than 0.18 may be considered to have a relatively small or large placenta. Any coefficient less than 0.08 or greater than 0.2 at term may be considered to be associated with an abnormally small or large placenta. The data are presented and discussed in respect to the clinical significance and applicability. It seems that marked deviations in the placental coefficient are associated with perinatal adversities.

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# A giant placenta

## A case report

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THE average placental weight is approximately 500 grams, or one sixth the weight of the child. Adair and Thelander<sup>1</sup> in their study of 392 placentas, found the average placental weight to be 473 grams with the greatest being 830 grams. Sinclair,<sup>2</sup> in his analysis of placentas from 1,443 live births, recorded weights varying from 120 grams to 975 grams. Ferguson<sup>3</sup> reported that 82 placentas, collected as controls in a clinical experiment, had an average weight of 466 grams. In syphilis, the placenta may weigh one fourth, one third, or even one half as much as the fetus. Large placentas have been observed in cases of erythroblastosis.

Since placentas weighing over 1,000 grams are apparently very unusual, it seems worth while to report this case.

In the literature from 1945 through August, 1958, there were reports of only 3 placentas weighing 1,000 grams or more. Chavigny<sup>4</sup> reported a normal placenta weighing 1,650 grams from a diabetic patient with kidney disease but with no evidence of Rh incompatibility or syphilis. A 1,000 gram placenta was reported by Magnin<sup>5</sup> in 1949 and a 1,080 gram placenta was reported by Riviere<sup>6</sup> also in 1949. Only in the case cited by Chavigny did the infant live. In these 3 cases the maternal serological test for syphilis was negative.

Mrs. R. L. F., a 26-year-old gravida v, para iii, Negro woman, was admitted to the Jackson Memorial Hospital on July 25, 1958, in active labor. The membranes had ruptured spontane-

ously shortly before arrival. The patient had received antepartum care elsewhere. Her weight on admission was 163½ pounds (76.3 kilograms), a weight gain of 13½ pounds during pregnancy. Other than a complaint of dizzy spells during the last 2 weeks of pregnancy, the patient had had no antepartum difficulties.

This patient's obstetrical history was unremarkable except for one spontaneous miscarriage at 3 months' gestation. All previous deliveries, reportedly normal, were attended by a midwife. The largest child had weighed 10 pounds at birth, the smallest child 9 pounds. The patient's last delivery was 2½ years previously.

Physical examination on admission to the hospital was not remarkable. The fundus was 36 cm. above symphysis pubis. The back was to the right with the fetal heart tone heard in the right upper quadrant at a rate of 144 per minute. The presenting part was thought to be breech and at Station minus 2; the cervix was 4 cm. dilated; the membranes had ruptured and the pelvis was thought to be adequate. A 3 plus pretibial edema was present.

Laboratory data showed hemoglobin to be 4.1 Gm. per cent which, after a thorough hematological work-up, proved to be an iron-deficiency anemia. Urinalysis was normal. Sick cell preparation was negative. Rh was positive and type was O.

A normal 2 hour, 8 minute labor terminated with a spontaneous delivery of a 3,836 gram (8 pound, 9 ounce) grossly deformed infant. The delivery of the baby was followed immediately and spontaneously by delivery of a placenta weighing 1,984 grams (4 pounds, 6 ounces). The anomalies of the infant included hydrocephalus and a large omphalocele. There was almost complete exstrophy of the entire abdominal contents. No cry was ever elicited. Respirations were poor and the infant died shortly after delivery.

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Fig. 1. Giant placenta; weight, 4 pounds, 6 ounces (1,984 grams).

On microscopic examination of the placenta no evidence of syphilis or any other pathological condition could be found. Special stains failed

to demonstrate Spirochetes. An autopsy was not performed on the infant.

Because of the suspected association of syphilis with unusually large placentas, this patient's past history was carefully reconstructed. In 1948, she was first diagnosed as having late congenital syphilis and received 3 adequate courses of penicillin in 1948, 1951, and 1955; her serological test for syphilis remained positive but low titer. A child born in 1953 had a negative serological test for syphilis. At the time of the present delivery the VDRL was weakly reactive, and the Kahn test 3 plus. The spinal fluid examined was negative. The patient also had a normal glucose tolerance test and blood urea nitrogen. The diagnosis was late syphilis, adequately treated, without sign of activity.

The patient received multiple transfusions and was discharged on oral iron therapy. Her subsequent health has been good.

#### Summary

This is a case report of an unusually large placenta, weight 1,984 grams, associated with infant anomalies in a woman with a past history of syphilis who, at the time of delivery, was cured of this infection.

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# Pregnancy complicated by diabetes

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DURING the past 3 decades increased knowledge in the management of pregnancy complicated by diabetes has all but eliminated the associated infertility, the increased frequency of early abortion, and the high maternal mortality rate. Interest now is focused primarily upon reducing the perinatal loss of viable infants born of diabetic mothers.

According to Jackson<sup>1</sup> the diabetogenic action of the increased levels of circulating adrenal corticosteroids provides additional stress to the pancreatic islet cells during pregnancy. In the potential diabetic this may give evidence of disease long before clinical diabetes would have become recognizable in the nonpregnant state. The obstetrician, therefore, is afforded an unparalleled opportunity to detect diabetes in its earliest stages.

## Material

On the obstetrical service of the Pennsylvania Hospital 81 viable pregnancies occurred in 58 diabetic patients during the 18 year period from 1940 through 1957. The incidence of diabetes complicating pregnancy during this period was 1 in 650 deliveries (Table I). The pregnancies were equally divided between private and service patients. Thirty-two pregnancies occurred in Negro patients and 49 in white patients. The youngest patient was 17 years of age and the oldest was 45. Ninety per cent of the pregnancies occurred in patients between the ages of 20 and 39 years. The

over-all perinatal mortality rate for the hospital during this period was 2.67 per cent.

Table I. Incidence of diabetes complicating pregnancy

No. pregnancies	No. diabetic patients	No. pregnancies in diabetic patients	Incidence
52,701	58	81	1:650

## Classification of severity

The degree of severity of diabetes associated with pregnancy has a direct relationship to the incidence of maternal complications and fetal survival rate. Several classifications, each of which has a place in the ultimate formulation of a plan of management for both the pregnancy and the complicating diabetes, have been proposed. Unfortunately a variance of opinion has resulted in a different standard being used in determining the degree of severity in each classification.

The oldest and probably the most widely utilized classification is that propounded by White and associates.<sup>2</sup> The severity of diabetes in this classification is based on historical data which include age at onset and duration of the disease, as well as the objective findings relating to the progression of vascular damage (Table II). White's classification was the first major contribution to a systematic approach to the evaluation of the severity of diabetes complicated by pregnancy and must necessarily remain fundamental to our understanding of this problem.

From the Pennsylvania Hospital.

Presented at a meeting of the Obstetrical Society of Philadelphia, Oct. 2, 1958.

Table II. Historical-vascular classification of severity of diabetes complicating pregnancy<sup>14</sup>

Class A	"Glucose tolerance test diabetes" or "chemical diabetes" requiring no insulin
Class B	Onset over age 20; duration less than 10 years; no vascular disease
Class C	Onset age 10-19; duration 10-19 years; minimal vascular damage
Class D	Onset under age 10; duration over 20 years; hypertension, retinitis, or minimal vascular sclerosis
Class E	Calcified pelvic vessels
Class F	Nephritis

Diametrically opposed to White's standards of severity is the group<sup>3, 4</sup> who believe that the degree of metabolic deficiency as measured by insulin requirements is the most important factor in judging severity of diabetes in pregnancy (Table III).

Table III. Classification of severity of diabetes complicating pregnancy according to insulin requirement

Mild	Dietary control; no insulin required
Moderate	Less than 50 units insulin required per day for chemical control
Severe	50 units or more insulin required per day for chemical control

Tolstoi, Given, and Douglas<sup>3, 4</sup> believe that even without long duration and the sequelae of vascular damage, the patient who is prone to ketosis and who requires large amounts of insulin to control this complication has severe diabetes. It would seem that this is particularly true when fetal survival is evaluated in relation to episodes of maternal ketosis.

More recently Pedowitz and Shlevin<sup>5</sup> have proposed a simplified classification based upon fetal risk (Table IV). It is generally agreed that renal damage or marked sclerosis of the pelvic vessels when associated with pregnancy complicated by diabetes offers increased fetal risk. Duration of the metabolic abnormality becomes a meas-

Table IV. Classification of severity of diabetes according to fetal and maternal risk

Unfavorable group	
A. Fetal	Renal insufficiency or extensive sclerosis of pelvic vessels
B. Maternal	Coronary disease or extensive retinopathy
Favorable group	
All other cases regardless of age of onset, duration, or insulin requirement	

urement of severity, from the obstetrical point of view, only if these organic changes are present. Maternal risk is increased when extensive retinopathy and coronary disease are present. This then becomes the unfavorable group in which there is unquestionably increased risk to either or both the fetus and the mother. Occasionally, pregnancy may be contraindicated in such patients. The favorable group consists of all other cases, regardless of age of onset, duration, or insulin requirements. It has been demonstrated<sup>6, 7</sup> that there is no significant difference in fetal salvage in patients requiring insulin and those not requiring insulin for control of diabetes. However, in the favorable group the fetal hazard will be increased if maternal ketosis develops. This complication does not depend upon duration of the disease or amount of insulin required, but rather upon faulty medical management or poor patient cooperation. This fact has been demonstrated dramatically by Pedersen and Brandstrup's<sup>8</sup> reported low fetal loss in their group of "long treated" patients who were hospitalized at 32 weeks' gestation or earlier and remained in the hospital under extremely careful medical supervision until delivery was effected.

In this study, when the patients were classified according to White's criteria of duration and age at onset of diabetes, all but 4 fell into relatively mild categories (Table V).

When the patients were classified according to their insulin requirement it was noted that 17 required no insulin. Forty-five required less than 50 units of insulin per day,

Table V. Historical-vascular classification

Class	No. pregnancies	Fetal loss	%
A	17	0	0
B	50	8	16
C	10	2	20
D	4	1	25
E	0	0	0
F	0	0	0

and 19 required 50 units or more of insulin per day for metabolic control of the diabetes (Table VI).

Classification of the patients according to the prognosis for fetal salvage or maternal risk or both, as suggested by Pedowitz and

Table VI. Classification according to insulin requirement

Insulin requirement	No. pregnancies	Fetal loss	%
Mild (no insulin)	17	0	0.0
Moderate (less than 50 units insulin)	45	6	13.3
Severe (50 units insulin or more)	19	5	26.3

Shlevin,<sup>13</sup> indicated that only one met the criteria for inclusion in the unfavorable group. This patient had severe diabetic retinopathy with retinal hemorrhages. The remaining 80 cases were classified as favorable (Table VII).

Table VII. Classification according to fetal and maternal risk

Risk	No. pregnancies	Fetal loss	%
Unfavorable group			
A. Fetal	0	0	0.0
B. Maternal	1	0	0.0
Favorable group	80	11	13.8

Prenatal care

Adequate prenatal care requires that the obstetrician constantly be alert for evidences not only of clinical diabetes but also of sub-clinical diabetes in its earliest recognizable form. Patients who give a family history of diabetes, a past history of large babies, of stillbirths, or of toxemia associated with

large babies or patients with postprandial glycosuria warrant postprandial blood sugar determinations or glucose tolerance tests.

When this complication of pregnancy becomes apparent it is imperative that a high degree of cooperation be established among the patient, obstetrician, internist, and pediatrician. To improve the liaison between physicians and patient, a special prenatal clinic for diabetic patients was established several years ago at the Pennsylvania Hospital. In this clinic all pregnant patients on the diabetic service are seen simultaneously by the obstetrician and the internist, coordinating all phases of diagnosis and therapy and establishing the greatest possible degree of rapport with the patient.

Patients are seen at 2 week intervals during the first 2 trimesters of pregnancy and at weekly intervals or more often, if necessary, during the final trimester. All patients in whom the diagnosis of diabetes is made during the current pregnancy and those whose known diabetes never has been evaluated fully or in whom the disease is poorly controlled are admitted to the hospital for intensive study. This includes an evaluation of the cardiovascular system, renal function tests in cases of diabetes of long duration or those with albuminuria, and x-ray studies of the pelvis for evidences of calcification of the uterine vessels. Diet and insulin requirements also are standardized at this time. The patients are given careful instructions in dietary principles, the use of insulin, and the testing of their urine. Patients who at any time during the pregnancy show evidence of ketosis, albuminuria, or complications of pregnancy are admitted to the hospital for further evaluation and intensive treatment.

Diet and insulin requirements which may vary during the pregnancy must be individualized to meet the nutritional and metabolic requirements of the patient. Duncan<sup>9</sup> has recommended that the basic diet be high in protein and somewhat liberal in carbohydrate. The basal caloric requirements are calculated by multiplying 10 times the patient's ideal weight in pounds



and adding 100 calories for pregnancy. To this is added an additional 30 per cent if the patient leads an active life. This total caloric intake is derived from 250 Gm. or more of carbohydrate plus 2 Gm. of protein per kilogram of body weight. The remaining calories are obtained from fat. The insulin requirement is adjusted to maintain careful chemical control of the blood sugar levels. At the present time a combination of NPH and regular insulin usually is given in the morning before breakfast. If the diabetes is of a labile type a small dose of NPH insulin is given again in the evening after supper. The patients are instructed to test the urine daily for sugar, and, if a 4 plus glycosuria is present, also to test for urinary acetone. This procedure will detect the presence of subclinical ketosis, and early treatment may be instituted to prevent more severe forms of acidosis. Common to all dietary regimens is a low sodium content and the addition of a multivitamin supplement. Diuretics such as chlorothiazide or acetazolamide are used if edema occurs. Meticulous attention to the details of prenatal care will aid in decreasing the incidence of pre-eclampsia and, if it should occur, will insure its early recognition and prompt treatment. No prenatal endocrine therapy was used in this series of cases.

#### Complications of pregnancy

As recorded in numerous other studies of diabetes complicating pregnancy, ketosis was the most common antenatal complication in this series of cases (Table VIII). It occurred in 20 cases (24.7 per cent) and was the chief contributing factor in 8 of the 11 fetal deaths.

There were 13 cases (16 per cent) of pre-eclampsia. Five of these were associated with varying degrees of maternal ketosis. There was one intrauterine fetal death which occurred in a patient with the combined complications of ketosis and pre-eclampsia. This patient was allowed to deliver spontaneously at full term. The other 4 patients with both ketosis and pre-eclampsia were delivered between the thirty-sixth and

**Table VIII.** Complications of pregnancy and delivery in diabetic patients

Complications	No. of cases	Fetal loss
Ketoacidosis	20	7
Pre-eclampsia alone	8	0
Pre-eclampsia with acidosis	5	1
Hydramnios	9	0
Abruptio placentae	3	1
Placenta previa	1	1
Premature labor	5	0
Premature rupture of membranes	3	0
Rh isoimmunization	2	1
Essential hypertension	3	0
Retinal hemorrhage	1	0
Fetopelvic disproportion	3	0
Pyelonephritis	1	0
Rheumatic heart disease	1	0
None	38	0

thirty-seventh weeks of pregnancy, and the babies survived. Conservative treatment of pre-eclampsia with a viable fetus seems to be a greater hazard to the infant than does early termination of pregnancy.

Hydramnios occurred 9 times in this series, and 2 fetal deaths occurred among these patients. However, in 1 there was severe fetal erythroblastosis culminating in a neonatal death, and in the other there was prolonged and uncontrolled maternal ketoacidosis. No babies born of mothers with hydramnios exhibited congenital abnormalities.

#### Termination of pregnancy

The termination of pregnancy prior to term has become an established principle in the management of diabetic pregnancies, and it is an important factor in the prevention of intrauterine fetal death. The risk of intrauterine death is negligible prior to the thirty-sixth week, provided the diabetes is well controlled and pre-eclampsia does not supervene. However, thereafter the incidence of intrauterine death rises rapidly.

The early termination of pregnancy can be a two-edged sword with the threat of prematurity and hyaline membrane disease on the one hand and early placental senescence with intrauterine death on the other.



Despite the dangers of prematurity it appears that the best perinatal fetal survival rates will be obtained when well-controlled diabetic pregnancies are terminated between the thirty-sixth and the thirty-eighth week of gestation. Those pregnancies with the additional complicating factors of pre-eclampsia, hypertension, recurrent ketosis, or renal disease will require even earlier termination.

In this study 34 patients were delivered between the thirty-ninth and fortieth weeks of pregnancy (Table IX). Thirty-six were

**Table IX.** Time of termination of pregnancy and associated fetal loss in diabetic patients

Week of pregnancy at time of termination	No. of cases	Fetal loss	
		Neonatal	Intrauterine
39th to 40th	34	1	3
36th to 38th	36	0	3
Prior to 36th	11	3	1

delivered between the thirty-sixth and thirty-eighth weeks and the remaining 11 prior to the thirty-sixth week.

**Mode of delivery**

Vaginal delivery is the method of choice if no fetopelvic disproportion exists and provided labor commences spontaneously or can be induced readily between the thirty-sixth and thirty-eighth weeks of pregnancy. However, since the criteria necessary for an easy induction followed by a short labor is encountered infrequently at this time of pregnancy, the procedure of choice becomes cesarean section in a large percentage of cases. Prolonged labor or traumatic delivery is associated with increased fetal mortality.

**Table X.** Method of delivery and associated fetal loss

Method of delivery	No. of cases	Fetal loss
Spontaneous vaginal	47	9
Induced vaginal	5	1
Cesarean section	29	1

In this group of patients, 52, or 64.2 per

cent, were delivered via the vaginal route (Table X). Labor was induced in only 5 cases. Delivery was accomplished prior to the thirty-ninth week in only 18 of these cases. There were 10 perinatal fetal deaths in the group who were allowed to deliver vaginally.

Cesarean section was elected as the mode of termination in 29, or 35.8 per cent, of the cases (Table XI). Three patients were delivered between the thirty-sixth and thirty-

**Table XI.** Associated indications for cesarean section in diabetic patients

Associated indications	No. of cases
Previous section	8
Primary section	21
"Unripe" cervix	11
Pre-eclampsia and acidosis	2
Previous large baby (traumatic delivery)	2
Previous fetal loss	1
Fetopelvic disproportion	2
Abruptio placentae	1
Placenta previa	1
Rh isoimmunization	1

eight weeks. Cesarean section was employed to deliver one patient at the thirty-second week because of placenta previa. This accounted for the only fetal death in this group. Diabetes plus associated factors including previous cesarean section, cervix not amenable to induction of labor, previous fetal loss, previous traumatic delivery, and pre-eclampsia or acidosis were the indications for cesarean section in 24 cases. Other indications included fetopelvic disproportion, abruptio placentae, placenta previa, and Rh isoimmunization.

**Care of the newborn**

The newborn of diabetic mothers must be managed as premature infants regardless of birth weight or gestational age. The physiologic function seldom corresponds to their weight or size. Immediately after delivery the infants should be placed under the supervision of a pediatrician skilled in the care of prematures. Such care is continued in the

premature nursery until the infant shows no further evidence of prematurity or additional neonatal problems including edema, lethargy, feeding difficulties, and hyaline membrane syndrome. These complications are dealt with according to current pediatric practice.

Perinatal mortality

The total number of perinatal deaths in this group of 81 diabetic pregnancies was 11 infants or 13.6 per cent. Seven of these deaths were stillbirths and 4 were neonatal fatalities.

A valid statistical analysis of these fetal deaths was not possible in this small series. However, certain impressions were gained as to the predominant causes of death and the corrective measures which might have prevented such deaths. When the fetal deaths were analyzed according to the historical-vascular classification it was found that 6 of the 7 stillbirths occurred in patients with mild diabetes (Table XII). The other stillbirth occurred in a patient whose diabetes was of long duration and with associated hypertension.

Table XII. Time and causes of perinatal mortality according to historical-vascular classification of severity of maternal diabetes

Class	Time of fetal death		Primary cause of fetal death
	Ante partum	Neo-natal	
B	6	1	Maternal ketoacidosis Placenta previa; prematurity
	0	1	
C	0	1	Abruptio placentae; prematurity
	0	1	Rh isoimmunization; prematurity
D	1	0	Maternal ketoacidosis

Of the 7 stillbirths, in all of which severe and recurrent maternal ketoacidosis was the primary cause of fetal death, the daily maternal insulin requirement was less than 50 units in 4 cases and more than 50 units in 3 cases (Table XIII).

Table XIII. Time and causes of perinatal mortality according to maternal insulin requirement

Insulin requirement	Time of fetal death		Primary cause of fetal death
	Ante partum	Neo-natal	
Less than 50 units per day	4	1	Maternal ketoacidosis Placenta previa; prematurity
	0	1	
50 units or more per day	3	0	Maternal ketoacidosis
	0	1	Rh isoimmunization; prematurity
	0	1	Abruptio placentae; prematurity

Analysis of the cases according to the prognosis for fetal or maternal salvage indicates that only one patient could be classified as an unfavorable risk (Table XIV). This patient had advanced retinopathy with retinal hemorrhages which was considered a maternal hazard. The infant was normal and it survived. All cases in which fetal death occurred were classified as favorable and thereby were at least theoretically preventable deaths. The primary cause for the 7 intrauterine fetal deaths was maternal ketoacidosis which must be considered a preventable complication of diabetic pregnancies. In 3 of these the ketoacidosis developed as the result of faulty diabetic control by the physician in cooperative patients. Poor patient cooperation, including failure to follow the diabetic regimen or late registration in the prenatal-diabetic clinic, accounted for the other 4 stillbirths. The one neonatal death resulting from maternal ketoacidosis occurred in a patient in whom the diagnosis of diabetes was made during the last month of pregnancy when the patient was already acidotic. The other 3 neonatal deaths resulted from prematurity associated with Rh isoimmunization, placenta previa, and abruptio placentae. These 3 cases must be classified as favorable from the diabetic aspect. However, the additional complications were probably the primary causes of the fetal deaths.

When the perinatal fetal deaths were ana-

Table XIV. Time and causes of perinatal mortality according to fetal risk

Risk	Time of fetal death		Cause of fetal death	
	Ante partum	Neonatal	Primary	Secondary
Favorable group	4	0	Maternal ketoacidosis	Uncooperative patient
	3	1	Maternal ketoacidosis	Faulty diabetic control*
	0	1	Rh isoimmunization	Prematurity
	0	1	Abruptio placentae	Prematurity
	0	1	Placenta previa	Prematurity
Unfavorable group	0	0		

\*Failure of diabetic control by physician.

lyzed according to the time of termination of pregnancy, it was noted that 6 of the 7 stillbirths occurred after the thirty-fifth week of gestation. Three of these occurred during the thirty-ninth and fortieth weeks. The other 3 occurred during the thirty-seventh and thirty-eighth weeks and all were associated with inadequately controlled diabetes. The seventh death occurred at the twenty-eighth week in a patient with juvenile diabetes who was also hypertensive and who experienced frequent episodes of ketoacidosis. Of the 4 neonatal deaths, one was in an infant delivered at full term with death a few hours after delivery attributable to maternal acidosis. Another was born at 34 weeks with death resulting from prematurity in an infant with Rh isoimmunization. The remaining 2 infants died of prematurity after delivery at 32 weeks; one death was due to placenta previa and the other was due to partial abruptio placentae causing premature labor and delivery.

#### Maternal mortality

There was one maternal death in this group of patients. This patient was 25 years of age, gravida viii, para vii. The heaviest previous baby weighed 6 pounds, 10 ounces and all previous babies were living and well. There was no family history of diabetes. She registered in the routine prenatal clinic at the thirtieth week of pregnancy and a diagnosis of diabetes complicating pregnancy was made. The patient failed to return to clinic following this initial visit and never received treatment for the diabetes. She was admitted to the hospital during the thirty-

sixth week of pregnancy in labor and in diabetic coma. The labor was of 12 hours' duration and was terminated by low forceps delivery. The infant was stillborn and weighed 7 pounds, 4 ounces. The patient never recovered from the coma and she died 68 hours post partum.

This maternal death was preventable and resulted from a combination of the patient's failure to return to the clinic for further evaluation and treatment, and an institutional failure to pursue an adequate follow-up effort on the patient. Obviously, a patient well advanced in pregnancy at the time the diagnosis of diabetes was made should have been admitted to the hospital immediately for complete study and institution of therapy. This death occurred prior to the establishment of the prenatal-diabetic clinic in this hospital.

#### Comment

It appears from the increasing number of reports in the literature that with strict chemical control of the maternal diabetes and meticulous prenatal measures to obviate obstetrical complications, a perinatal mortality rate of less than 10 per cent will become attainable in almost all well-run obstetric clinics. Equally and possibly more important is the excellent opportunity for the obstetrician to detect maternal diabetes in its earliest preclinical and clinical forms. The simple expedient of performing post-prandial blood sugar determinations or glucose tolerance tests on all patients in whom there is a suspicion of diabetes is all that is required for initial detection.



The correct management of the pregnant diabetic patient is dependent upon the proper classification of the severity of the diabetes. It would seem that when diabetes associated with pregnancy is being evaluated, the degree and location of premature vascular aging is more important than the amount of insulin required for chemical control or the duration of diabetes alone. Duration of the metabolic disturbance then becomes significant only if there are sclerotic changes in the uterine arteries or nephritis with increased fetal risk or coronary artery disease or retinopathy with increased maternal risk. The simplified classification of severity as proposed by Pedowitz and Shlevin, based on fetal and maternal risk as related to the arteriosclerotic changes, appears to be admirably suited to the problem of pregnancy complicated by diabetes.

Analysis of the perinatal deaths and the maternal death indicates the necessity for further education of the laity and the profession. Emphasis is focused also upon the need for strict cooperation between the patient and her physicians.

The over-all perinatal fetal mortality rate was 13.6 per cent. When the so-called pre-clinical or "glucose tolerance test" cases of diabetes were eliminated the fetal death rate was 17.2 per cent. However, it is doubtful whether these 17 cases of preclinical diabetes should be eliminated from the statistics used to compile the perinatal mortality rate. It has been clearly shown by other investigators<sup>10-13</sup> that the fetal loss prior to the clinical recognition of diabetes equals or

exceeds that occurring in patients with known diabetes.

The diagnosis of diabetes was made during the current pregnancy in 30 cases in this series. Among this group were 6 fetal deaths, accounting for more than one-half of the total fetal loss. Recognition of the diabetes was made during the last trimester in 4 cases. The primary cause of fetal death was severe maternal ketosis in all 6 cases. These findings serve to emphasize further the need for early recognition and careful chemical control of diabetes during pregnancy if there is to be an improvement in the fetal salvage rate.

#### Summary and conclusions

1. Pregnancy as a form of diabetogenic stress to the maternal pancreatic islet cells is discussed.

2. The need for adoption of a simplified classification of the severity of diabetes based upon the additional obstetrical risk is emphasized.

3. The highest perinatal fetal survival will be accomplished when well-controlled diabetic pregnancies are terminated between the thirty-sixth and the thirty-eighth week and earlier when complicated by recurrent ketosis, pre-eclampsia, hypertension, or renal disease.

4. The total perinatal fetal mortality in this study is 13.6 per cent. Probably the most important factor for improvement of fetal salvage is the full understanding by both patients and physicians of the necessity for well-planned and complete prenatal care.

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# Idiopathic thrombocytopenic purpura and pregnancy

Report of 5 new cases and review of the literature

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THE purpose of this paper is to evaluate the obstetrical problems presented by a patient with a history of idiopathic thrombocytopenic purpura. Should such a patient be advised to conceive? If she is pregnant, should interruption be advised? Should splenectomy be done during pregnancy? What is the fetal prognosis? The pertinent literature and additional cases have been reviewed in an attempt to answer these questions.

## Historical review

Arand<sup>1</sup> described the first case of purpura in pregnancy in 1765. Barnes<sup>2</sup> and Byrne<sup>3</sup> each reported cases of purpura during pregnancy in 1867. Barnes's case, almost certainly a secondary purpura, has many times since been cited as the earliest report. His unfortunate result of premature labor with neonatal and maternal death was to set the grave tone in all reports during the subsequent 75 years. Dohrn<sup>4</sup> reported the first case of purpura in a newborn infant in 1873.

Many advances were made in the hematologic aspects of idiopathic thrombocytopenic purpura after 1842, when Donne<sup>5</sup> first described blood platelets. These ad-

vances made it possible to differentiate among various forms of purpura. Nevertheless, obstetricians continued to classify all cases of purpura associated with pregnancy in a single group. Fetal and maternal prognoses based on these reports were most grave. Mosher<sup>6</sup> stated, "only occasionally a patient goes to term and recovers." He believed that in one half the cases the fetus perished. Rushmore,<sup>7</sup> frequently quoted in obstetric and hematologic textbooks, reported fetal and maternal mortality rates of over 50 per cent in cases of purpura and pregnancy. Neither author made any attempt to distinguish among the various forms of purpura.

The first attempt to evaluate the results of pregnancy associated with true idiopathic thrombocytopenic purpura was made by Burnett and Klass<sup>11</sup> in 1943. They concluded that this combination was not necessarily fatal. Robson and Davidson,<sup>35</sup> agreeing with the importance of differentiating among the purpuras, concluded that the mortality in pregnant women with idiopathic thrombocytopenic purpura was no higher than could be expected from idiopathic thrombocytopenic purpura itself.

Slaughter and associates<sup>40</sup> reviewed cases of idiopathic thrombocytopenic purpura and pregnancy with special reference to splenectomy. They concluded that any infant born to a mother with thrombocytopenia, whether or not splenectomy had been done, would have thrombocytopenia.

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### Diagnosis

The prognosis and therapy in a pregnant patient with idiopathic thrombocytopenic purpura depend on an accurate hematologic diagnosis. Idiopathic thrombocytopenic purpura is diagnosed when *spontaneous bleeding* is associated with: (1) thrombocytes less than 100,000; (2) increased capillary fragility; (3) increased clot retraction time; (4) increased bleeding time (possibly normal); and (5) decreased serum prothrombin consumption.

In addition, the following must be normal: (1) Marrow biopsy, with the exception of immature megakaryocytes; (2) coagulation and prothrombin times; (3) blood levels for calcium, fibrinogen, Vitamin C, and Vitamin K; and (4) white and red blood cell counts in proportion to the amount of bleeding.

There must also be an absence of: (1) a family history of bleeding; (2) a history of recent infection or the absorption of toxins; (3) splenomegaly or adenopathy; and (4) lymphocytosis or abnormal cells in the peripheral blood.

### Case reports

**Case 1.** (No. 38077, F.H.) S. B. L. was seen in September, 1947, with purpuric spots of 6 months' duration. The platelet count was 80,000; the clot retraction time and capillary fragility were increased. Bleeding, coagulation, and prothrombin times were normal; peripheral blood and sternal marrow were normal. Pregnancy occurred in October, 1948, and was uneventful except for the occasional occurrence of purpuric showers. Platelet count on Feb. 17, 1959, was 72,000. Twin girls were delivered on June 16, 1949, in the thirty-seventh week of pregnancy. An immediate postpartum hemorrhage of 1,250 c.c. occurred. This patient returned in the fourth postpartum week with a secondary hemorrhage and at curettage retained placental tissue was found.

Both babies appeared normal. Unfortunately, platelet counts were not done on the mother or the children.

**Case 2.** (No. 51157, F.H.) K. K. was seen in September, 1950, with skin petechiae. The platelet count was 94,000; the bleeding time

and capillary fragility were increased; clotting and prothrombin times were normal; peripheral blood and sternal marrow were normal. Periods of remission and exacerbation occurred during the ensuing 2 years and pregnancy occurred in 1952. There were no exacerbations during pregnancy and no studies were done. Spontaneous delivery with minimal blood loss occurred on July 30, 1958. Maternal platelets counted on the day of delivery were 80,000. The baby appeared normal and the platelet count was 160,000.

**Case 3.** (No. 50981, F.H.) I. S. was seen during the sixth month of her fourth pregnancy because of epistaxis, hematuria, and peripheral petechiae. She had 3 children, presumably normal. The platelet count was 24,000; the bleeding time and capillary fragility were increased; clot retraction was absent; clotting and prothrombin times were normal; peripheral blood and sternal marrow were normal. She was delivered spontaneously with minimal hemorrhage on July 11, 1953. Maternal platelets on the first postpartum day were 84,000. The baby appeared normal and had a platelet count of 68,000 on the day of birth. This increased to 170,000 on the seventh day.

**Case 4.** (No. 226794, B.I.H.) R. A. was seen first in the seventh month of her second pregnancy because of skin and mucosal petechiae. Splenectomy had been done at age 16 following vaginal hemorrhage at the menarche. The first pregnancy had been interrupted in its ninth week without sequelae. The platelet count was 40,000; the bleeding time and capillary fragility were increased; the coagulation time was normal; peripheral blood and sternal marrow were normal. Spontaneous delivery with minimal bleeding occurred on Feb. 1, 1948, two days after a platelet count was reported as 10,000. The baby had numerous petechiae and two patches of ecchymosis over the sacrococcygeal area. A platelet count was not done. The patient was seen again on July 19, 1949, when she again was delivered spontaneously with minimal bleeding. There was no clinical evidence of purpura in mother or child. Blood studies were not done.

**Case 5.** (No. 245373, B.I.H.) S. S. was seen in March, 1949, because of menorrhagia and skin petechiae. She had one child, who was delivered 5 years previously. The platelet count was 10,000; the bleeding time and capillary fragility were increased; clot retraction was

absent; clotting time, peripheral blood, and sternal marrow were normal. Splenectomy was done on July 5, 1949. She was delivered spontaneously with minimal bleeding on July 6, 1951. There was no clinical evidence of purpura in mother or baby. Blood studies were not done.

#### Analysis of reported cases

The literature was searched and individual case reports evaluated. Fifty-three women<sup>8-48</sup> were accepted as having had a reasonably accurate diagnosis of idiopathic thrombocytopenic purpura made either before or during a pregnancy. The 5 cases reported above were added to give a total of 58 patients with 72 deliveries and 73 fetuses. There was one twin birth.

**Maternal mortality.** There were 4 maternal deaths, a rate of 5.5 per cent. Two occurred in the fourteenth week of pregnancy as a result of cerebral hemorrhage. A third patient had a splenectomy performed during the sixth month of pregnancy. Severe postoperative shock and loss of fetal heart tones followed. Spontaneous delivery occurred on the seventh postoperative day and death from purpura occurred 4 days later. The fourth death occurred as a result of sepsis and purpura following a splenectomy performed in the early postpartum period.

**Fetal mortality.** Sixty-one babies were delivered alive and well, a rate of 83.5 per cent. Two fetuses were lost when the mothers died in the first trimester. One fetus died after elective hysterotomy performed at 6½ months of pregnancy. The corrected fetal salvage rate is then 87.1 per cent.

Three babies died in utero in the immediate postsplenectomy period. Three babies died of purpura. One baby with purpura died of a tentorial tear after elective low forceps delivery. One baby died of atelectasis after cesarean section performed because of toxemia. One baby died of prematurity.

**Delivery without splenectomy.** Twenty-six pregnancies were terminated without prior splenectomy (Table I). There were either manifestations of purpura or thrombocytopenia during each pregnancy. Three

**Table I.** Pregnancy terminated without prior splenectomy

<i>Pregnancies (26)</i>	
Purpura or thrombocytopenia present during pregnancy	26
Deaths	3
Cerebrovascular accident in early pregnancy	2
Splenectomy in early postpartum period, sepsis	1
Postpartum hemorrhage	4
Sulcus tear	1
Retained placental tissue	1
Uterine atony	2
Premature separation of placenta	1
Premature labor	1
Cesarean section	3
Obstetric indication and simultaneous splenectomy	2
Splenectomy for purpura and simultaneous hysterotomy	1
<i>Fetuses (27)*</i>	
Previa	3
Purpura or thrombocytopenia at birth	16
Purpura absent; platelets not reported	6
Purpura absent; platelets normal	2

\*Includes one twin delivery.

women died. Postpartum hemorrhage occurred four times, once as a result of retained products of conception and once as a result of a sulcus tear. Premature separation of the placenta, premature labor, and twin delivery each occurred once. Cesarean section was done three times. In 2 cases the indication was purely obstetrical, and splenectomy was done at the same time.

There were 27 fetuses. Three, all previa, died. Sixteen babies had clinical manifestations of purpura or thrombocytopenia. Six babies had no evidence of purpura but, unfortunately, platelet counts were not reported. Two babies had no clinical evidence of purpura and had normal platelet counts.

**Splenectomy prior to pregnancy.** Twenty-one patients who had splenectomy performed prior to pregnancy had 34 babies (Table II). Seven of these patients had no clinical evidence of purpura and/or thrombocytopenia during 10 pregnancies. Nevertheless, one baby died of purpura and three others had purpuric manifestations. Two babies had no purpura but did have throm-



Table II. Splenectomy prior to pregnancy

Purpura or thrombocytopenia absent during pregnancy	10 (7 patients)
Baby died of purpura	1
Baby lived with purpura and/or thrombocytopenia	5
Baby without purpura, platelets not reported	4
Purpura or thrombocytopenia present during pregnancy	24 (14 patients)
Baby died of purpura	3
Baby lived with purpura and/or thrombocytopenia	17
Baby without purpura, platelets not reported	2
Baby without purpura, platelets normal	2
Total pregnancies	34 (21 patients)

bocytopenia. Four babies without purpura had no platelet counts reported.

Fourteen patients had clinical purpura and/or thrombocytopenia at some time during 24 pregnancies. (Four patients with 6 pregnancies are included here although the authors fail to report whether or not such existed.) Two babies died of purpura and one with purpura died of a tentorial tear. Seventeen babies had purpura or thrombocytopenia. Two babies had no purpura, but platelet counts were not reported. Two babies had no purpura and normal platelet counts.

**Splenectomy during pregnancy.** Splenectomy was performed during pregnancy in 12 patients (Table III). In 3, the fetal heart tones disappeared in the immediate postoperative period. Of these, one had premature separation of the placenta and cesarean section was performed 8 days after splenectomy; one was delivered a stillborn infant spontaneously; and one died from idiopathic thrombocytopenic purpura. Premature delivery with living infants occurred twice, and one of these infants died subsequently of prematurity. Of 8 babies that survived, 3 had clinical purpura; 4 had no purpura, but platelet counts were not reported; and one had a normal platelet count

and no evidence of purpura. The mother of this last baby received cortisone during exacerbations of idiopathic thrombocytopenic purpura in this pregnancy.

**Postpartum splenectomy.** Splenectomy was performed in the early postpartum period four times. One patient died of sepsis and purpura.

**Corticosteroids during pregnancy.** Four patients received ACTH or cortisone during the antepartum period. All were delivered normally and the babies had no clinical purpura. One baby had no platelet count. Splenectomy was performed prior to pregnancy in one patient, during pregnancy in one patient, and in the late postpartum period in 2 patients.

Table III. Splenectomy during pregnancy

Patients	12
Death	1
Premature separation of placenta (postpartum)	1
Premature labor	2
Babies	12
Death	4
Intrauterine, postoperative	3
Prematurity	1
Purpura at birth, lived	3
Purpura absent, platelets not reported	4
Purpura absent, platelets normal	1

Prognosis

Should a patient with a history of idiopathic thrombocytopenic purpura be advised to conceive? If she is pregnant, should the pregnancy be interrupted? The answer to both questions depends on the incidence of maternal complications and the maternal mortality rate. Premature separation of the placenta and postpartum hemorrhage did not occur more often in the collected cases than would be expected in any unselected group of pregnancies. The maternal mortality of 5.5 per cent is no greater than could be expected from a group of nonpregnant patients with idiopathic thrombocytopenic purpura. Thus, pregnancy may be advised in the patient with a history of idiopathic thrombocytopenic purpura, and pregnancy



should not be interrupted because of idiopathic thrombocytopenic purpura.

Should splenectomy be performed during pregnancy? Primarily this decision rests with the hematologist. It is important, however, that the obstetrician point out that fetal death in utero, after splenectomy, occurs 25 per cent of the time and that premature labor and even maternal death may occur. If the disease can be controlled by medical means until the late postpartum period, splenectomy could then be done without concern for fetal well-being, without the added technical problems presented by the presence of a gravid uterus, and when the patient is physically and emotionally prepared.

What is the chance of fetal survival? The hematologic status of the baby must be evaluated immediately after birth and during the early days of life, despite previous splenectomy or the occurrence or absence of purpura or thrombocytopenia during the pregnancy. Clinical evidence of purpura and/or thrombocytopenia was present in 65 per cent (44 of 68) of the

babies born alive. Only 5 babies were proved to have normal platelet counts at birth. The disease in the baby is transient, and survival past the early neonatal period depends on therapy begun early. It is essential, therefore, that the obstetrician be fully aware of this responsibility for the newborn.

### Conclusions

1. A patient with a history of idiopathic thrombocytopenic purpura may be advised to conceive.

2. Interruption of pregnancy because of idiopathic thrombocytopenic purpura is not indicated.

3. Splenectomy in the pregnant patient is dangerous to both mother and baby. When possible, splenectomy should be postponed until the late postpartum period.

4. Neonatal purpura may occur when the mother has a history of idiopathic thrombocytopenic purpura despite previous splenectomy or the antepartum presence or absence of thrombocytopenia or purpura.

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#### Discussion

DR. WILLIAM F. FINN, Manhasset, New York.—Dr. Tancer stressed the problem which has arisen of distinguishing between the symptomatic and the true idiopathic purpuras. The symptomatic purpuras are usually due to injection or ingestion of various toxins, and they, fortunately, are not as severe as the idiopathic. Most of the idiopathic cases which are seen in clinical practice have already been recognized long before and have usually been treated by splenectomy.

Though these patients have a tendency to bruise easily and they have the abnormalities of their blood picture, they show surprisingly little hemorrhage at the time of delivery, and the hemorrhage is due to laceration rather than the low platelet count.

This question of splenectomy during pregnancy has been debated. At one time it was rather strenuously advocated. At the present time, I think the conservative opinion expressed by Dr. Tancer is being adopted more and more. Actually, the effects are very dramatic. The platelets show a rise from levels in the range of, say, 20,000 to 50,000 to up above 200,000 to 400,000.

I think this is one place where there should be a very intimate working relationship between hematologist and pediatrician and obstetrician. Certainly the pediatrician should be available, and he should immediately, in conjunction with the hematologist, take over the care of the baby. Most of the congenital thrombocytopenic purpuras which occur are transient and not serious.

# The nephrotic syndrome in pregnancy

## A case report

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THE nephrotic syndrome is a rare complication of pregnancy, occurring in from 0.1 per cent<sup>3</sup> to 0.028 per cent of pregnancies.<sup>6</sup>

"The nephrotic syndrome is a clinical state characterized by the excretion into the urine of 3.5 Gm. or more of protein per day, with double refractile and oval bodies. There is, in addition, a variable tendency towards edema, hypoproteinemia, and hyperlipemia, possibly dependent upon the amount and duration of the protein loss."<sup>2</sup>

There is little, if any, hematuria, pyuria, or azotemia. The blood pressure is usually normal.

The significance of renal disease associated with pregnancy is debatable. Addis<sup>1</sup> states that he has seen no evidence where the renal lesion interfered with pregnancy or was harmed by it. Speert and Guttmacher<sup>5</sup> think that chronic renal disease is a contraindication to pregnancy because it often results in exacerbation of the renal lesion. If pregnancy is allowed and the renal lesion becomes worse, prompt termination of the pregnancy is indicated.

Dieckmann's experience<sup>3</sup> has not been favorable in patients with renal impairment, as the fetal loss is high and the lesion may show progression.

The following is a case report of the nephrotic syndrome appearing in the second trimester of pregnancy. The appearance of the syndrome at this stage of gestation might suggest toxemia, but the diagnosis of nephrotic syndrome was based on the presence of edema, proteinuria, hypo-

proteinemia, and hypercholesteremia, without hypertension or azotemia.

Mrs. G. L., aged 34 years, was admitted to St. Francis Hospital on July 21, 1958, with the history of progressive edema of 4 weeks' duration and a weight gain of 17 pounds during the preceding 2 weeks despite a low-salt diet and therapy with Chlorothiazide and parenteral mercurial diuretics.

The past history was pertinent only in that the patient had a presacral neurectomy for dysmenorrhea and multiple myomectomies in 1955 and a spontaneous abortion in the same year. She exhibited signs of adrenal cortical hyperfunction, i.e., menstrual irregularity, anovulatory menstruation, acne, hirsutism, and an enlarged clitoris. She was treated for infertility with hydrocortisone, and later with a long-acting progestational substance (Delalutin, 7.0 Gm.). The latter therapy was followed by the present pregnancy. There was no history or evidence of previous renal disease. The last menstrual period was Feb. 11, 1958. Weight on admission was 147 pounds and there was pitting edema to the umbilicus.

The pertinent findings are summarized in Table I. The serum chlorides, CO<sub>2</sub> combining power, cephalin flocculation, phenolsulphophthalein excretion, test for lupus erythematosus cells, nonprotein nitrogen, and blood count were normal, as was the chest x-ray examination. The urine showed albuminuria with 2 to 3 white blood cells per high-power field.

Treatment was begun on the second hospital day with methylprednisolone (8.0 mg. every 6 hours) and continued for 12 days without diuresis. At this time, ACTH therapy (80 units intramuscularly twice a day), was substituted,

Table I. Summary of findings and treatment

	Date															
	5/28	Hospitalized								9/10	10/10	Hospitalized			1/14	2/4
		7/21	7/23	7/25	8/4	8/5	8/9	8/14	8/18			11/12	11/14	11/19		
Blood pressure																
Systolic	120	130	120	120	120	120	120	120	120	120	120	120	120	120	120	120
Diastolic	70	70	70	70	70	70	70	70	70	70	70	70	70	70	70	70
Weight	126	147	147	150	147	147½	140	134	134	126½	135	139½	126		117	116
Urine																
Albumin	0	+	++	+	+	+		+	+	++	++	±	±		0	0
Protein per 24 hours (Gm.)			12.0	7.2				8.0		6.8		.160			.97	
Serum (Gm. %)																
Cholesterol	210	744	670	440	490				406			362	330			220
Protein		3.4	3.8			3.6		4.2	4.2		4.6	4.6	4.6			5.8
Albumin		1.8	2.3		1.5	1.8		2.2	2.2		1.35	2.9	2.9			4.65
Globulin		1.6	1.5		1.8	1.8		2.0	2.0		3.25	1.7	1.7			1.15
A/G ratio		1.1	1.5			1.0		1.0	1.0		0.41	1.7	1.7			4.0
Treatment		Medrol, 8.0 mg. every 6 hours				ACTH, 80 units twice a day				ACTH, 80 units 3 times a week		Medrol, 8.0 mg. twice a day			Medrol, 4.0 mg. daily	

and prompt, marked diuresis resulted. The patient was discharged from the hospital on Aug. 19, 1958, weighing 134 pounds, to continue on ACTH therapy (80 units 3 times a week), and a low-salt, high-protein diet.

The patient was readmitted to the hospital on Nov. 12, 1958, for termination of her pregnancy by cesarean section in the thirty-eighth week of gestation. She was delivered on the following day of a healthy, apparently normal male infant, which weighed 5 pounds, 1 ounce and showed no detrimental effects of the maternal prenatal steroid therapy. ACTH therapy was discontinued on admission to the hospital, and methylprednisolone (4.0 mg. twice a day) was initiated. She was discharged on the sixth postpartum day, to continue the methylprednisolone (4.0 mg. two times a day) and a low-salt, high-protein diet. The dosage was reduced to 4.0 mg. on January 14 and was discontinued on Feb. 4, 1959. At this time the patient appeared to be in complete remission from the nephrotic syndrome. Her weight was 116 pounds, blood pressure 110/70, and the urine showed no abnormal elements.

Comment

There are only a few reports in the literature concerning the nephrotic syndrome in

pregnancy. Posner and associates<sup>4</sup> described a patient who was in the nephrotic stage of chronic glomerulonephritis when she became pregnant. She was delivered of a full-term, healthy infant after steroid therapy, and she continued to be free of edema after delivery.

Wegner<sup>6</sup> reported 3 cases, each of which pursued a different course. The first patient progressed from the nephrotic syndrome into glomerulonephritis and was delivered of a macerated fetus in 1927; she died in 1934. In the second case, the nephrotic syndrome appeared during each of 2 pregnancies, and complete regression occurred after delivery. The third patient, with the nephrotic syndrome in pregnancy, after 2 apparently normal pregnancies, succumbed to peritonitis of unknown cause following her third pregnancy. His conclusion is that pregnancy must be considered a real hazard for a woman with known nephrosis or nephrotic tendency.

The seriousness of the nephrotic syndrome is, of course, related directly to the etiology of the renal lesion. Addis<sup>1</sup> states that this syndrome is the direct result of chronic glomerulonephritis in over 90 per



cent of cases. Berman and Shreiner<sup>2</sup> think that it is wrong to assume nephrotic syndrome in adults is the result of chronic glomerulonephritis, and that the etiological factor is important because of therapeutic and prognostic implications.

The list of known causes of the nephrotic syndrome grows progressively larger and includes, among others, poststreptococcal glomerulonephritis, disseminated lupus erythematosus, amyloidosis, periarteritis nodosa, bilateral renal vein thrombosis, Kimmel-Stiel-Wilson disease, Tridione and Paradi-one therapy.

The use of renal biopsy, with examination under the electron microscope, is the most accurate method to establish the eti-

ological diagnosis of this condition. This is important as the use of steroids in all cases of the nephrotic syndrome is not indicated. When widespread, irreversible destruction of the glomeruli produces azotemia; the response to steroids is often adverse and may lead to uremia.<sup>3</sup>

No attempt was made to establish an etiological factor in this case by renal biopsy because of the pregnancy.

### Summary

A case of the nephrotic syndrome as a complication of pregnancy has been presented along with a brief review of the literature which contains but few references to this condition.

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# Intestinal obstruction in pregnancy

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THE purpose of this presentation is to review the problem of intestinal obstruction in pregnancy, based upon material from the Department of Obstetrics and Gynecology of St. Vincent's Hospital during the 16 year period from 1943 through 1958. Six cases were found among 39,231 deliveries, giving a ratio of 1.5 per 10,000 deliveries or 1 per 6,553.5 deliveries.

Although the symptoms and signs of obstructions in the intestinal tract are almost the same in the pregnant and in the non-pregnant state, pregnancy will, many times, obscure the symptomatology. Nausea, vomiting, constipation, and vague abdominal cramps in the first half of pregnancy tend to mask the symptomatology and, in many instances, may fatally delay the diagnosis. In the second half of pregnancy, the diagnoses of toxemia, constipation, Braxton Hicks contractions, or even "hysteria" may be made.

## **Etiology**

The first and most common cause of obstruction are adhesions and bands, that form after previous abdominal operations. In our material, postoperative adhesions contributed to obstruction in 5 of the 6 cases. It must be emphasized that extreme alertness should be exercised in any case where a woman who has had a previous abdominal operation presents vague abdominal symptomatology.<sup>4</sup>

Other etiological factors are volvulus, intussusception, hernias, miscellaneous causes

(e.g., openings in mesentery or broad ligament), and pregnancy ileus, in that order of frequency. With the uterus displacing the abdominal contents, it is perhaps surprising that there are not more cases of intestinal obstruction. The general decreased tonus, as well as the succulency of the intra-abdominal organs may contribute to the avoidance of more acute abdominal catastrophes. There was only one fatality in our 6 cases, although some of this material antedates the contemporary management of intestinal obstruction. Decompression, management of hemoconcentration, restoration of the electrolyte and fluid balance, and the use of antibiotics have helped considerably in decreasing the fatality rate. The factor of correct early diagnosis must be re-emphasized, however. Once the diagnosis has been made, the treatment is surgical after gastrointestinal decompression and restoration of the fluid and electrolyte balance is carried out. Needless to say, operation is not necessary if there is definite proof that the measures undertaken have led to restoration of the bowel patency.

## **Case reports**

**Case 1.** This patient was a 34-year-old white woman, gravida iii, para ii, who was admitted in the thirty-eighth week of pregnancy with the complaints of generalized abdominal pains of crampy character and tenderness in the right flank for several hours.

In 1939 she had had a Simpson-Montgomery uterine suspension for "adherent retroversion." In 1941 she had been delivered of a 6 pound, 10 ounce infant.

After 24 hours of observation, the patient still had the same type of pains and she continued to

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vomit. It was felt that the condition suggested an acute appendicitis, but "the soft abdomen without tenderness, absence of fever, indicated wisdom of watchful waiting." A laparotomy was performed 48 hours after admission and a loop of the terminal ileum was found obstructed by mesenteric adhesions in the upper right quadrant posterior to the uterus. This distal part of the intestines was found to be collapsed. The adhesions were cut and the bowels resumed their normal color. Wangenstein drainage was left in for 48 hours. After 30 hours flatus and fecal material were passed. On the sixth postoperative day a full-term male infant was delivered by low forceps.

**Case 2.** This patient, a 34-year-old gravida i, para 0, Negro woman, was admitted in the thirty-sixth week of pregnancy with abdominal cramps, constipation, and vomiting.

In 1933 she had had an appendectomy, and in 1946 a Simpson-Montgomery uterine suspension and left salpingo-oophorectomy with freeing of pelvic adhesions. One week postoperative a second laparotomy for intestinal obstruction was performed. A kinked loop of bowel was found to be adherent to the posterior uterine wall. The patient was readmitted 5 times in the next 2 years with symptoms of "chronic intestinal obstruction." The symptoms subsided repeatedly on conservative treatment.

At the time of this admission, decompression by Miller-Abbott tube and Wangenstein drainage, as well as restoration of the electrolyte and fluid balance, were sufficient to relieve the symptoms. However, 2 weeks later she was readmitted with recurrent signs of obstruction. A laparotomy was performed and a low flap cesarean section was done first with the delivery of a full-term, live infant. On later inspection, 2 firm adhesions were found fixing a loop of the small bowel to the posterior uterine wall and to the broad ligament. This loop was kinked and discolored. The adhesions were cut, and the bowel loop resumed its normal appearance. The postoperative course was uneventful. The patient had a repeat cesarean section in 1953. There has been no recurrence of obstruction.

**Case 3.** This patient, a 26-year-old white woman, gravida i, para 0, was admitted in the twenty-ninth week of pregnancy. A sudden onset of severe epigastric pain, retching, and vomiting occurred 8 hours before admission. There was one bowel movement on the day of admission.

Past history showed that in 1946 she had had an appendectomy for acute diffuse suppurative appendicitis.

On admission, the patient looked acutely ill, was vomiting green bilious material, but had a normal temperature and blood pressure. The uterine fundus was 4 fingers above the umbilicus, soft, and without contractions. On the following day a scout film of the abdomen showed ". . . few abnormally gas distended loops of bowel above the uterus which showed fluid levels probably indicating an obstructing lesion. . . ." Fifty-six hours after onset of symptoms a laparotomy was performed and an "adhesive band extending from the cecum to the ileum" was found. A loop of ileum approximately 4 feet long was caught by this band. The band was cut and the affected intestines recovered after 20 minutes. A Miller-Abbott tube was introduced and attached to the Wangenstein drainage. The postoperative course was uneventful.

Eleven weeks postoperatively, the patient was delivered of a term infant by low forceps. Two years later she had another uneventful delivery at term.

**Case 4.** A 23-year-old white woman, gravida ii, para i, was admitted in the twenty-ninth week of pregnancy. She had first been seen in the Emergency Ward complaining of severe epigastric pains of 6 hours' duration. This had been diagnosed "hysterical"; she was given 100.0 mg. of Demerol and sent home. Nine hours later, she was admitted with the same complaints.

There was no history of previous abdominal operation. She had been treated for symptoms of a peptic ulcer 7 years previously. There was apparently a recurrence of the gastric attacks every year. Her previous pregnancy had been uneventful.

Shortly after admission she started vomiting coffee-ground material and passed a tarry stool. Her blood pressure was 130/80 mm. and temperature 99.4°. The abdomen was "soft, without rebound or localized tenderness." The uterus was compatible with a pregnancy of 7 or 8 months, without contractions. The diagnosis on admission was: "hysteria; rule out acute abdomen. Not in labor." Twenty-four hours later the patient was still vomiting and complaining of the same epigastric pain. Seventy-two hours later she had a tarry stool. Shortly thereafter it was found that her blood pressure was 80/60 mm. Hg, pulse 160, and the general appearance was that of shock. The uterus was contracting,

with pains coming every 2 to 3 minutes. A surgical consultation was requested, and the consultant's impression was that of "uncontrollable emesis, and to rule out intestinal obstruction." The restoration of the fluid and electrolyte balance, as well as decompression, was recommended. A Cantor tube was passed and attached to Wangenstein drainage.

Ninety-six hours after admission she was delivered precipitously of a stillborn, premature (1,000 grams, 38 cm.) fetus in breech presentation. Because of the critical condition of the patient the placenta was not removed and was expelled 34 hours later.

At this time, chlorides were 490 mg. per 100 c.c., blood urea nitrogen 74 mg. per 100 c.c., CO<sub>2</sub> 49 vol. per cent. The abdomen became progressively more distended. The impression was now one of "generalized spreading peritonitis, etiology unknown." Five days after admission a diagnostic scout film showed "fluid in the peritoneal cavity consistent with peritonitis." Death occurred 48 hours later.

Postmortem examination revealed "Intussusception of the ileum at the site of Meckel's diverticulum, with gangrene and generalized peritonitis."

**Case 5.** This patient, a 42-year-old white woman, gravida viii, para vi, who had had one abortion, was admitted in the twenty-fourth week of pregnancy with complaints of abdominal pains and vomiting starting early on the morning prior to admission.

In 1940 she had had an appendectomy; in 1950, a cholecystectomy. From 1935 through 1947 she had had 6 spontaneous full-term deliveries.

Physical examination revealed a moderately obese woman with the pregnant uterus extending one finger above the umbilicus. There was a definite tenderness in the left upper quadrant, as well as left costovertebral angle tenderness. Four days later, a scout film of the abdomen showed "multiple fluid levels in the jejunum, consistent with intestinal obstruction most likely due to adhesions." The next day, a Miller-Abbott tube was introduced. After 2 days she started passing flatus, and 4 days later she had a spontaneous bowel movement.

Three months later she was delivered spontaneously of a full-term, live infant. Examination 2 weeks later showed no evidence of recurrent intestinal obstruction.

**Case 6.** A 25-year-old white patient, gravida iii, para i, who had had one ectopic pregnancy,

was admitted in the twenty-eighth week of pregnancy with severe progressive low abdominal pains, backache, and vomiting of 3 hours' duration. This pregnancy had been uneventful until admission.

Past history revealed a full-term forceps delivery of a live 10 pound infant 3 years before and unilateral salpingo-oophorectomy for ruptured tubal pregnancy 2 years previously. On admission, the abdomen was moderately distended with slight tenderness over the left lower quadrant and mild tenderness and rebound throughout. The uterine fundus was approximately 2 fingers above the umbilicus, the uterus soft, not contracted, and no fetal heartbeat audible. An x-ray examination of the abdomen showed: "Single intrauterine fetus of approximately 7 months' gestation. . . . Several small collections of small bowel gas in the epigastrium, right upper quadrant, and left flank. Colon virtually free of gas. . . . The appearance of these short scattered, small bowel loops suggests the changes of an enteritis or early obstruction."

A Cantor tube was passed and a scout film 24 hours later showed a slight increase in the dilatation of the previously described small bowel loops. Thirty-six hours after admission, the patient was delivered spontaneously of a premature 3 pound, 6 ounce live infant, and this appeared to relieve the condition temporarily. The abdomen remained moderately distended, however, with no bowel sounds or flatus. The tip of the Cantor tube was still in the stomach. An operation was performed on the same day and an adhesive band was found strangulating the root of the mesentery. A large area of ileum affected by this constriction was completely gangrenous and proximal segments of the small bowel were greatly distended. A large amount of turbid, pink-colored fluid was found in the abdominal cavity. The tip of the Cantor tube was palpable in the stomach cavity. Approximately 100 cm. of ileum was resected and a lateral anastomosis performed. Pathohistologic diagnosis was gangrene. The immediate postoperative course showed slight improvement. A Miller-Abbott tube was passed instead of a Cantor tube and better drainage was obtained. However, the patient's condition deteriorated again on the third postoperative day with appearance of diffuse abdominal tenderness. Roentgenogram showed "localized paralytic ileus with a possibility of a subdiaphragmatic inflammatory process." On the fifth postoperative day she had



a brownish bowel movement after an enema. Simultaneously she developed a sharp pain in the right hemithorax followed by moderate dyspnea. Chest x-rays suggested "pneumonitis or pleural effusion or both at right base, as well as paralytic ileus of moderate degree." Because of a confusing clinical picture suggesting a peritonitis with a possible subphrenic abscess and intestinal obstruction, a laparotomy was again carried out. The operative findings at this time were those of generalized peritonitis, with the intestines matted together by fairly firm adhesions and adherent to the anterior abdominal wall. Two loops of jejunum appeared to be excessively angulated. There was no evidence of a subdiaphragmatic abscess. No collapsed loops of intestine were found. The adhesions were freed and loosened, and the peritoneal cavity drained. This postoperative course was complicated by a bilateral pneumonic consolidation in the lower lobes. The patient recovered and was discharged on the nineteenth day after the second laparotomy.

#### Comment

Many points in these cases merit comment. In 5 out of 6 cases, there was a history of previous abdominal operation and in these 5 cases the obstruction was secondary to postoperative adhesions or bands. All obstructions were of small bowel type and in 5 patients the obstruction occurred during the third trimester. The remaining patient had obstruction in the twenty-fourth week.

Some investigators<sup>2</sup> have pointed out that the absence of rigidity, tenderness on palpation, and distention are almost pathognomonic in the early stages of obstruction in pregnancy. However, this is also a common observation in all cases of early small bowel obstruction regardless of pregnancy. In analyzing this material we found a tendency to search for distention as a sign of obstruction. Distention, however, appeared only in the later stages, whereas rigidity, rebound, and localized tenderness may be encountered earlier but are not necessarily characteristic of obstruction.

In some of the cases there was hesitancy in diagnosing the condition because the pa-

tient had passed fecal material or flatus in the beginning. Any fecal material or gas present in the distal bowel, however, can be expelled until that area is completely empty.

There is usually no fever, leukocytosis, or signs of shock in the early stage of a simple obstruction. These signs appear only later as secondary manifestations of dehydration, hemoconcentration, loss of electrolyte balance, and infection. One of the most important procedures in the early diagnosis is the x-ray examination. Although occasionally inconclusive, in many instances it might show distinct changes within a few hours of the first symptom.

Procrastination is particularly detrimental in strangulation. Whereas a simple obstruction can be treated adequately for several days with the proper therapeutic measures, strangulation, unless diagnosed and treated early, will lead to bowel gangrene.

The presence of a pregnant uterus may be an impediment in making the diagnosis since pains are often confused with uterine contractions. However, in these cases there was no appreciable uterine irritation at the onset of symptoms. In two of the patients labor ensued in the advanced stages of obstruction.

Once the diagnosis is established, treatment consists of intestinal decompression and restoration of electrolyte and fluid balance. These procedures have helped decrease the mortality from 40 per cent 30 years ago to 10 per cent at the present time.<sup>3</sup> Although gastric suction may afford some relief, it is necessary to bring the tip of the tube as close to the proximal site of the obstruction as possible. Once decompression has been achieved, the most aggravating symptoms, vomiting and cramps, usually subside. Although, in isolated cases of an incomplete or intermittent obstruction, this management alone has restored bowel patency, in the majority of cases the obstruction is still present. Another factor contributing to procrastination is the reluctance to open the abdomen in the presence of a

gravid uterus because of the danger of provoking premature labor. However, with gentle management and necessary precautions, the pregnancy can be preserved in almost all instances. A delay in operating might be necessary in advanced cases of hemoconcentration, electrolyte and fluid imbalance, and shock. With proper decompression and restoration of the body fluid balance, operative risk is improved. The only exception where immediate operation is indicated is that of strangulation.

Intussusception during pregnancy has been recognized as one of the most fatal complications of bowel obstruction, and the case here reported was no exception. In 1937 Chaffin and associates,<sup>1</sup> in describing their own case, reviewed the world literature and found 12 cases during pregnancy, 2 during labor, and 6 in the puerperium. Of 21 patients, 15 died. Most of the reviewed cases belonged to the era before the con-

temporary diagnostic and therapeutic facilities were available, and the mortality of 75 per cent is persistent testimony of the great danger of this complication.

### Summary

Six cases of small bowel obstruction in pregnancy are described. In 5 the obstruction was due to postoperative bands or adhesions. Among them was one case of strangulation, necessitating a wide resection of ileum. Four patients were operated upon, while in one the restoration of patency was achieved by conservative management.

There was one fatality; this was in a case of intussusception at the site of Meckel's diverticulum diagnosed at autopsy.

We would like to express our appreciation to Drs. T. Iovino, R. Lowrie, C. Immordino, and W. Gage for permission to use their private cases for this report.

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# Inferior vena cava syndrome in late pregnancy

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AS EARLY as 1924, Runge<sup>1</sup> made the observation in women who were in the late stage of their pregnancy that the venous pressure was higher in the leg than in the arm and that after these women delivered, the vein pressure in the leg fell. In 1942, Hansen<sup>2</sup> observed that in the last month of pregnancy there is a marked predisposition to circulatory collapse in the supine position and that this disturbance disappears when the patient turns to the left lateral position. Brigden, Howarth, and Sharpey-Schafer,<sup>3</sup> in their studies of the effect of posture on peripheral blood flow, noted that when the venous pressure in the legs of a woman in late pregnancy was measured with a condenser manometer, it was found that the pressure rose 7.5 cm. in the supine position and fell when the subjects were turned slightly to one side. They concluded that in late pregnancy the uterus may obstruct the veins of the abdomen when the subject is in a strictly supine position and cause a rise of venous pressure caudally and a fall in pressure in the right auricle. The exact site of venous obstruction was not determined.

Holmes,<sup>4</sup> in 1957, reviewed the literature concerning sudden deaths caused by circulatory collapse following spinal anesthesia for cesarean section. Some details of the circumstances leading to the fatal circulatory collapse in 17 cases revealed a pattern in which "sudden death" occurred some minutes after the patient had been placed in the supine position following the administration of a spinal anesthetic.

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The interval depended on the analgesic drug employed and was closely related to the time which the agent in question usually required to produce sympathetic block of the thoracic segments. Furthermore, the circulatory failure was not immediately appreciated since cessation of respiration was usually the first untoward sign observed. For these patients, resuscitative measures were ineffective. The author concludes that the high venous pressure in the lower extremities of these pregnant patients at term is probably due to the pressure of the enlarged uterus on the inferior vena cava and that this interference with venous return to the heart will produce a fall in cardiac output and arterial pressure.

## The syndrome

Classically, the inferior vena cava syndrome manifests itself in pregnant or nonpregnant patients when either intra- or extra-abdominal pressure on the inferior vena cava decreases the return circulation to the heart, resulting in reduced cardiac output and blood pressure. The patient feels faint, is pale, and may be nauseated. If the pressure is relieved or, in the case of pregnancy, the patient is turned from the supine position onto the left side, return circulation improves and the blood pressure approaches pre-syndrome levels.

## Rationale of treatment of inferior vena cava syndrome in late pregnancy

Treatment is directed toward relieving the pressure from the inferior vena cava. It has been our practice to place some folded sheets

under the right hip, which results in tilting the pelvis and uterus to the left side.

### Illustrative case report

S. D., 32. The significant previous history described an earlier cesarean section which was complicated postoperatively by a severe pulmonary infarct. During the last few weeks of the pregnancy, the patient complained of light-headedness and nausea when lying flat on her back.

She was given premedication consisting of Seconal, 50 mg., two hours and Demerol, 50 mg., and scopolamine, 0.4 mg., one and a half hours prior to the scheduled time of the cesarean section. The initial blood pressure of the patient while lying supine on the operating table was 60/40 with a pulse of 108. She complained of severe nausea and light-headedness. The patient was turned to the left lateral position and the next blood pressure reading was 110/60. She was rechecked in the supine position and the blood pressure reading fell to 80/40. The patient was turned again to the left lateral position and epidural anesthesia was administered at L-3-4 interspace with use of a 22 gauge needle and 2 per cent Xylocaine solution with 1:200,000 epinephrine. After a test dose of 3 ml. had been injected, an additional dose of 14 ml. of the same solution was instilled. The patient was turned to the supine position. Some folded sheets were placed under the right hip to maintain a slight left lateral tilt. The anesthesia level reached to T-8. Subsequent blood pressure readings ranged between 120-100/60 prior to the delivery of the newborn and 140/60-70 after the delivery. Anesthesia, operation, and post-operative course progressed satisfactorily.

### Comment

It is the aim of this report to bring to the attention of physicians a consideration of the problem of the inferior vena cava syndrome. Howard, Goodson, and Mengert<sup>5</sup> have

quoted an incidence of supine hypotensive syndrome of 11.2 per cent of patients at term. In our experience of 2,000 patients undergoing cesarean section at or near term, the incidence of severe inferior vena cava syndrome (systolic less than 80) has been less than 1 per cent. The diagnosis of the syndrome as described above is relatively easy to make and confirm. It is our contention that, if the usual small dose of regional anesthesia for cesarean section is utilized and an effort is made to tilt the pelvis toward the left lateral position, no more than slight circulatory embarrassment will result. In the main, we agree with the conclusions reached by Holmes.<sup>4</sup> However, taking into consideration the anatomical position of the inferior vena cava we believe it is more logical to tilt the patient to the left rather than to the right lateral position to correct the circulatory embarrassment. In practice it would appear that our method has been more effective.

The occurrence of the inferior vena cava syndrome in nonpregnant patients has been encountered occasionally, when subjects are placed in extreme Buie or right lateral high kidney bar positions, when excessive packing has been used during intra-abdominal operations, etc. A discussion of these cases is felt to be beyond the scope of this paper.

### Summary

A brief historical review of the inferior vena cava syndrome in late pregnancy has been presented. Reference has been made to its occurrence in certain operative positions. The syndrome has been described and discussed. An illustrative case report is presented and a simple remedy is offered for the treatment of this syndrome.

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# Carcinoma of the cervix and pregnancy

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THE true incidence of carcinoma of the cervix associated with pregnancy is difficult to establish. Reports from many institutions include patients referred specifically for this condition as well as cases occurring in registered obstetric patients. Such figures would not reflect the true frequency with which carcinoma of the cervix occurs during pregnancy. Hayden,<sup>3</sup> in a compilation of figures from 7 reports, found that carcinoma of the cervix occurs in 0.024 per cent of pregnancies. This represents one case of carcinoma of the cervix in about 4,000 obstetric patients. By a similar summation of figures, the same author points out that pregnancy complicates 1.8 per cent of carcinoma of the cervix.

Previous reports are in agreement that the clinical stage of the neoplasm at the time of therapy is the most important guide to prognosis, as it is in the nonpregnant patient. Whether or not the associated pregnancy alters the prognosis has been the subject of much discussion. Since many of the reports are based on relatively few cases, observations concerning the possible influence of pregnancy on carcinoma of the cervix have infrequently had the support of statistical validity. In addition, Way<sup>13</sup> has pointed out that the prognosis of carcinoma of the cervix in women under 40 may be less favorable, stage for stage, than the prognosis in older patients. Since most of the pregnant patients with this neoplasm

are under the age of 40, any effect of pregnancy on prognosis can be demonstrated only by comparing the results of therapy with those obtained in nonpregnant patients of the same age group and with disease of the same extent. With these factors in mind, Sadugor and his associates<sup>10</sup> studied the results in therapy in 124 patients with carcinoma of the cervix associated with pregnancy. They concluded that the results did not differ from those in nonpregnant patients. Others have also pointed out that pregnancy does not seem to alter prognosis in carcinoma of the cervix.<sup>3, 6, 7, 9, 14</sup> On the other hand, Holzaepfel and Elzell,<sup>4</sup> Kistner,<sup>5</sup> and Danforth<sup>1</sup> have suggested that pregnancy has a deleterious effect on carcinoma of the cervix, especially when the neoplasm is treated in the latter part of pregnancy and in the puerperium.

## Material

The present study is restricted to those patients in whom carcinoma was discovered during pregnancy or within 4 months following delivery or abortion. Only those patients receiving their primary therapy at the Indiana University Medical Center or Marion County General Hospital are included. Thirty such patients have been treated from 1940 through 1958. Because all 21 patients encountered at the Indiana University Medical Center were referred specifically for treatment of carcinoma of the cervix, they cannot be equated against obstetric patients registered in this institution to calculate an incidence rate. The 9 cases from

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the Marion County General Hospital occurred in obstetric patients registered from 1950 through 1958. During this time, there were 19,904 obstetric admissions. Thus, in this hospital, carcinoma of the cervix occurs once in approximately 2,200 pregnancies. As Eastman points out, race and environmental factors will probably influence the frequency with which carcinoma of the cervix occurs in the obstetric patient.<sup>2</sup>

The youngest of the 30 patients was 22 years of age, while the oldest patient was 43. The average age was 31.8 years. The average parity of these patients was 4.4, and no nulliparous patients were encountered in this series. In 7 patients, the diagnosis of carcinoma was established within 4 months following delivery, while in one patient the neoplasm was detected 2 months after spontaneous abortion in the first trimester of pregnancy. The remaining 22 patients were pregnant at the time carcinoma of the cervix was discovered. No cases of intraepithelial carcinoma are included in this study. All neoplasms were of the epidermoid type. Table I illustrates the distribution of cases by International Stage and the duration of pregnancy upon discovery of the neoplasm.

Table I. Distribution of cases by trimester and stage

Stage	Trimester			Post partum
	First	Second	Third	
I	2*	6	8	4
II	1	1	1	1
III	1	1	3	0
IV	0	0	0	1

\*In one case diagnosis of carcinoma of the cervix was established after first trimester abortion.

### Symptoms

Abnormal bleeding was the presenting symptom in 26 (87 per cent) of the patients. The remaining 4 patients were asymptomatic and, in 2 of these patients, the diagnosis of carcinoma was established on the first antenatal visit by biopsy of a

suspicious lesion of the cervix. In the remaining 2 patients, cervical lesions were present which were thought to be benign, but cytologic preparations demonstrated abnormal cells. Subsequent biopsy revealed carcinoma. Cytologic preparations are now utilized routinely in the antenatal clinics of both hospitals. This screening procedure has already been of aid in the diagnosis of early carcinoma of the cervix in the asymptomatic obstetric patient.

### Delay in diagnosis

One of the striking features found in review of cases during the current study was the frequency of physician delay in establishing the presence of a carcinoma of the cervix during pregnancy. Montgomery<sup>8</sup> has found that such delay occurs twice as often in pregnant patients as it does in nonpregnant individuals. From statistical studies, such as those of Todd,<sup>12</sup> it seems probable that a patient's chances for successful treatment of carcinoma of the cervix decrease about 15 per cent for each month that treatment is delayed after the onset of vaginal bleeding.

Of the 21 patients referred to Indiana University Medical Center for treatment of carcinoma, physician delay occurred in 13 cases (62 per cent). Delay was considered to have occurred when one or more months elapsed between onset of bleeding due to carcinoma and subsequent diagnosis. The longest delay was 14 months, while the average delay was 4.5 months. In this group, only 11 patients had Stage I lesions when therapy was begun, while carcinoma had spread beyond the cervix in the remaining 10 patients (48 per cent).

In marked contrast were the 9 patients from Marion County General Hospital where antenatal care is under the supervision of obstetric resident physicians. Physician delay (5 weeks) occurred in only one case. All 9 of these patients had neoplasms classified as clinical Stage I and, in 4 of these, sections from conization specimens gave evidence of very early invasion of stroma. Although all of these patients are

not eligible for 5 year survival figures, it is gratifying to note that 8 of the patients are alive and apparently free from carcinoma at the time of this report. One patient died of cancer 18 months after treatment.

An analysis of the reasons for physician delay indicated that vaginal bleeding was attributed to threatened abortion or other obstetric complications without benefit of examination to eliminate the cervix as the source of bleeding.

Delay in diagnosis of carcinoma of the cervix associated with pregnancy can be minimized if the following principles are observed:

1. On the initial antenatal visit, cytologic studies of the cervix are carried out in all patients. Suspicious lesions of the cervix are immediately biopsied.
2. Cold knife conization as a hospital in-patient procedure is carried out if: (a) punch biopsy reveals the presence of intra-epithelial carcinoma; (b) repeated cytologic preparations reveal abnormal cells in the presence of a grossly normal cervix.
3. Vaginal bleeding at any stage of pregnancy prompts inspection of the cervix with repetition of cell study or biopsy if the latter is indicated.
4. Biopsy or cytologic study precedes cauterization of lesions of the cervix at the time of postpartum examination.

### Therapy

Primary radiation therapy for carcinoma of the cervix is favored. The following principles of therapy are suggested according to the stage of gestation in which the diagnosis of carcinoma of the cervix is made. On occasion, procedures may be modified to satisfy religious principles.

**First trimester.** External radiation is carried out until a depth dose of 2,000 r is reached at point A and 3,000 r at point B. This is administered over approximately a 3 week span and abortion often occurs during the second or third week of treatment. External therapy is followed by radium application by means of the Manchester technique. This segment of therapy

adds 6,500 or more gamma r to point A and an additional 2,000 gamma r to point B. If abortion does not occur during external therapy, the uterus is emptied by curettage and the first radium application is made on the seventh postoperative day.

**Second trimester.** Since fetal tissues are now less sensitive to radiation, abortion is unlikely to occur as a result of external therapy. Therefore, the uterus is emptied by abdominal hysterotomy and external radiation is begun on the seventh postoperative day. During therapy, the wound is protected by a lead strip. At the completion of external radiation, central radiation in the form of radium is provided as before.

**Third trimester.** Prompt treatment of carcinoma of the cervix discovered at 29 or 30 weeks' gestation will enhance the patient's chances to survive this disease. Delivery at this time will usually result in neonatal death from immaturity. If the patient, cognizant of the risk to the fetus, agrees to treatment, classic cesarean section is carried out with external radiation and radium therapy following in that order. If the patient and her family desire to delay treatment in deference to the unborn child, classic cesarean section is carried out at about 34 weeks; this is followed by radiation treatment. If carcinoma of the cervix is discovered after the thirty-fourth week of pregnancy, immediate classic cesarean section is advisable, and this is to be followed by radiation as outlined before.

**Post partum.** Radiation therapy of carcinoma of the cervix discovered in the postpartum period is managed as if the patient had not been pregnant.

### Results of therapy

Five or more years have elapsed since the treatment of 16 of the 30 patients reviewed in this study. Table II compares the survivals in this group with nonpregnant individuals under 40 years of age treated during the same period of time from which the study cases were drawn. Although the survival rates of pregnant patients in Stages I and II are lower than those in nonpreg-

Table II. Five year survival

Stage	Nonpregnant			Pregnant		
	No.	No. sur- viving	% sur- viving	No.	No. sur- viving	% sur- viving
I	24	20	83	9	6	67
II	42	21	50	3	1	33
III	16	4	25	3	0	0
IV	8	0	0	1	0	0

Table III. Five year survival by duration of pregnancy

Stage	First and second trimesters			Third trimester and post partum		
	No.	No. sur- viving	% sur- viving	No.	No. sur- viving	% sur- viving
I	1	0	0	8	6	75
II	1	1	100	2	0	0
III	2	0	0	1	0	0
IV	0	0	0	1	0	0

nant patients of comparable stages, this difference is not of statistical significance in this small group. Table III demonstrates an apportionment of the patients eligible for 5 year study into two groups. The first

group was treated during the first and second trimesters of pregnancy and the second group was treated during the third trimester of pregnancy and the postpartum period. No influence of duration of gestation upon survival rates can be identified.

Summary

Thirty cases of carcinoma of the cervix associated with pregnancy have been reviewed and discussed in relationship to the frequency of coincidence of these conditions as well as the age and parity of the patients involved. Symptomatology has been discussed briefly. Delay has been discussed and the means of reducing delay in diagnosis have been outlined. A general outline of radiation therapy of these patients has been presented and the results of therapy have been discussed briefly.

Conclusion

The chief threat to the pregnant patient with carcinoma of the cervix is not alteration of the biologic behavior of the neoplasm by pregnancy, but the delay that may occur before the carcinoma is detected.

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# Pseudomonas aeruginosa as a cause of necrotizing renal papillitis

## Case report

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AN ENTITY seldom diagnosed ante mortem is necrosis of the renal papillae or, as termed by Davson and Langley,<sup>1</sup> "papillitis renis necroticans." Usually, this condition is discovered at autopsy and it occurs more frequently in diabetic than in nondiabetic patients.<sup>2</sup> von Friedrich<sup>3</sup> in 1877 first mentioned the occurrence of papillary necrosis of the kidney which he thought might be the result of pressure atrophy occurring in association with hydronephrosis. A later report from Schömer<sup>4</sup> concerning this disease entity suggested that the starting point of the process was in the center of the pyramid, while Foulon<sup>5</sup> believed that in his case necrotic renal papillae were the result of tumor tissue compressing the vessels, thus causing ischemia of the renal tips. Mellgren and Redell,<sup>6</sup> however, observed necrotizing pyelonephritis with bilateral necrotizing papillitis in two nondiabetic patients. In these cases, the authors considered the predisposing cause to be deposition of a paramyloid substance in the vessels, which reduced the capillary blood supply, anatomically known to be the poorest in the kidneys. The precipitating cause, in their opinion, was a bacterial poisoning. More recently, Robbins<sup>7</sup> thought necrotizing renal papillitis to be, rather, a form of acute pyelonephritis. Little has been reported to date in the literature concerning the bacterial path-

ogenesis of this disease entity, therefore a review of our case seems pertinent.

A 25-year-old white married woman, gravida ii, para 0, who had had one abortion, entered the University Hospital on Aug. 5, 1958, for elective cesarean section. Uteroplasty had been performed 2 years prior for bifid uterus. The expected date of confinement was Aug. 12, 1958. A recent x-ray film had shown a normal mature fetus. Prenatal history revealed a 20 pound weight gain, intermittent traces of albumin and sugar in the urine, and in the last trimester recurrent 2-plus pedal edema. Diuretics had been administered only once. Orthostatic hematuria had been noted for the last 4 to 5 months. On admission urinary bladder examination was negative, with the kidneys to be evaluated later. No chills, fever, diabetes, or allergies were noted. Her father had died of "kidney disease"; her mother was alive and well. Physical examination disclosed a well-oriented patient in no obvious distress. Organs were essentially normal with the uterus enlarged to the size of a full-term pregnancy. Temperature was 98° F., pulse 82, respirations 16 per minute, and blood pressure 132/72. No albumin or sugar was present in the urine, but many red blood cells, 2 to 5 white blood cells, and a few epithelial cells were seen on microscopic examination. Protein was 30 mg. per cent. Laboratory data are shown in Table I.

**Hospital course.** On Aug. 7, 1958, after catheterization, the patient was given medicine and prepared for operation. A cesarean section was performed and a full-term viable male infant was delivered. The postoperative course for the first 8 days passed uneventfully with only slight headaches thought to be due to

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spinal anesthesia. To determine the cause of the prenatal orthostatic hematuria, a flat plate of the abdomen was taken on August 11 and revealed no stones. A concurrent intravenous pyelogram disclosed ureteral contraction and dilatation thought to be due to the pregnancy. It was noted at the time of genitourinary examination that the patient had passed two tiny stones. On August 14 the more detailed inspection of this flat plate revealed a left ureteral calculus and another genitourinary consultation was scheduled for August 15. During this examination the catheter could not be passed beyond the obstruction. The patient had evidenced chills prior to the procedure, and a temperature of 104.2° F. was reported on her return to her room. The patient was obviously septic and toxic with a range in temperature of 103.8° to 104.2°, pulse 138 to 160, and blood pressure 70/50 to 90/60. Two units of whole blood, 500 c.c. of normal saline, and 1,000 c.c. of 5 per cent glucose in water, Levophed, and 11 million units of penicillin were administered. Ureteral lithotomy was deferred temporarily until adequate antibiotic levels were reached. On August 17 the patient's condition was worse. With an apical rate of 188 and pulmonary edema in evidence, a phlebotomy was performed, and

approximately 700 c.c. of blood was withdrawn. At noon the same day the patient was taken to the operating room for removal of the obstructing stone. At 12:44 P.M. the phonocardiograph became silent and at 12:52 P.M. the chest and pericardium were opened, manual cardiac massage instituted, and Adrenalin given at which time ventricular fibrillation appeared and was counteracted with potassium and electroshock "successfully." The left ureter was the size of an index finger and under abdominal pressure urine appeared. An indwelling catheter was left in the ureter and the patient died in the operating room. Necropsy was performed 2 hours after death.

**Bacteriology report.** An antemortem blood culture showed growth of *Pseudomonas aeruginosa*; an antemortem urine direct smear, amorphous debris, many pus cells, no organism; antemortem urine culture, two varieties of *Ps. aeruginosa* colonies. Postmortem blood culture showed growth of *Ps. aeruginosa*; Postmortem BUN was 59 mg. per cent, creatinine, 5.1.

**Necropsy findings.** The left kidney was swollen and weighed 230 grams. The paper-thin capsule stripped with ease, revealing a dark reddish granular outer surface studded with multiple yellowish abscesses 1 to 2 mm. in size. On

Table I. Laboratory data

<i>Blood</i>				
Date	Aug. 5	Aug. 8	Aug. 16 (A.M.)	Aug. 16 (P.M.)
Hematocrit (%)	32	—	33	41
Hemoglobin (Gm.)	10.7	11.7	10.7	13.2
White blood cells	8,550	11,400	27,150	14,450
Nonsegmented cells	19	25	64	89
Segmented cells	57	59	27	6
Total neutrophils	77	84	91	55
Lymphocytes	21	13	9	13
Eosinophils	1	1	—	—
Basophils	—	1	—	1
Monocytes	1	1	—	—
<i>Urine</i>				
Date	Aug. 6	Aug. 7	Aug. 16	
pH	6.0	7.0	—	
Protein	30	—	Trace	
White blood cells	2-5	Occasional	5-20	
Red blood cells	Many	25-30	Occasional	
Epithelial cells	Few	Moderate	Occasional	
Sugar	—	—	Trace	
<i>Blood chemistry</i>				
Date	Aug. 16			
BUN	35 mg. per 100 ml.			
Sodium	139 mEq. per liter			
Potassium	4.5 mEq.			
Chloride	102 mEq.			

section most of the papillae were necrotic, and at the base of the pyramids a fine wavy zone of inflammation separated viable from necrotic tissue. The papillae were soft and yellowish in color. The cortex was filled with numerous small yellow abscesses. The calices and pelvis were fiery red with a granular edematous surface, and a finger-sized ureter was filled with abundant creamy green, purulent liquid material extending down to the obstructing calculus 3 cm. proximal to the ureteral bladder opening. An indwelling catheter was found above the obstructing calculus in the ureter. The urinary bladder contained an estimated 50 c.c. of urine similar to that found in the left ureter. There was marked acute hemorrhagic cystitis. The right kidney was not remarkable. The spleen was somewhat enlarged, rather soft, mushy, and dark red on section. The heart showed two electrocoagulated surface areas on the anterior left ventricular wall. No thrombus was found in the pulmonary vessels. All lung lobes were collapsed. The uterus was of postpartum status with a recent intact operative wound and was partially filled with clotted blood and fragments of deciduous tissue. The stomach was distended because of gaseous content.

Microscopically the involved kidney showed suppurative pyelonephritis. One section showed a necrotic papillary tip and exhibited a zone of inflammatory reaction which was found at the base of the pyramid. In the cortex numerous convoluted tubules were filled with polymorphonuclear leukocytes and bacterial emboli with foci of necrosis. The necrotic centers of these tubules contained numerous predominantly mononuclear cells. The glomeruli were unaffected except those of suppurative involvement. Other tubules were filled with eosinophilic material. In the necrotic papillae the tubules were stuffed with debris or bacterial colonies with recognizable rod forms. Some tubules showed good preservation, with little or no leukocytic response to these necrotic foci. No vasculitis or vessel thrombosis was seen.

This was a case of unilateral renal papillary necrosis in a woman suffering from *Pseudomonas aeruginosa* septicemia and left acute suppurative pyelonephritis with obstructing calculus in the left ureter. The patient died of ventricular fibrillation during operation.

### Comment

The pathogenesis of this lesion has interested pathologists for many years. Günther<sup>2</sup> thought that in some of his investigated cases papillary necrosis was caused by *Bacillus coli* and staphylococcus organisms. Davson and Langley<sup>1</sup> were under the impression that the *B. coli* may have a direct toxic effect on the renal tips. Edmondson,<sup>8</sup> however, thought that the coagulase enzyme of the Staphylococcus and Menkin's necrosin factor together might be responsible for the necrosis. Robbins and Angrist<sup>9</sup> believed that bacterial toxins alone could not be responsible. Levaditi<sup>10</sup> produced renal papillitis artificially by the introduction of vinylamine or tetrahydroquinone into animals. He suggested a special affinity of this poison for the renal papilla. Baldwin and co-workers described hemolytic *Staph. aureus* renal infections in diabetes. According to Hand,<sup>12</sup> who quotes Kerby's analysis of the source of *Pseudomonas* sepsis, the site of entrance for the organism in pelvic and urinary infections occurred in 6.8 per cent of 83 investigated cases through the external genital organs. Stanley<sup>13</sup> supported this view and added that the frequent presence of this organism on the anogenital skin region facilitates implantation into the urinary tract, particularly in women. Instrumental manipulation and obstruction in and about the urinary tract are already known predisposing factors. Positive antemortem blood cultures associated with clinical signs of sepsis support the hypothesis of hematogenous spread of this organism after introduction of contaminated instruments, fluids, or drugs into other parts of the body. This has been well described by Scott<sup>14</sup> in his investigation of 82 cases of blood stream infections in urology. Other various predisposing factors for *Pseudomonas aeruginosa* sepsis include disturbance or alteration of bacterial flora in the intestinal tract by drug administration, diminution of resistance to bacterial invasion in the presence of debilitating diseases; enhancing bacterial virulence in humans by repeated passage

with probable reduction of immune response to antibiotic therapy.<sup>12</sup>

Clinical findings in our case agree with findings in other cases described by various authors, although, in our case, the immediate cause of death was cardiac arrest and ventricular fibrillation during operation. Stirling<sup>15</sup> reports 4 cases of necrotizing renal papillitis in childhood with one patient suffering from *B. pyocanea* septicemia. Robbins and Angrist<sup>9</sup> report a total of 26 cases of necrotizing renal papillitis but mention only one case with *Ps. aeruginosa* involvement in a diabetic patient with no urinary obstruction.

After a search of the literature, it would appear that this case is unique in showing necrotizing renal papillitis due to *Ps. aeruginosa* in a nondiabetic adult with unilateral urinary obstruction. *Ps. aeruginosa* septicemia was also present as shown by positive blood cultures both ante and post mortem.

### Summary

1. A case of renal papillary necrosis with suppurative pyelonephritis in a nondiabetic adult with a left unilateral calculus urinary obstruction is reported as a unique occurrence.

2. Pathogenesis of this disease entity is discussed with emphasis of bacteriological aspects.

3. Pathologically, the lesion is well recognized and described.

4. Antemortem clinical diagnosis of this disease is rarely made and only if considered in the presence of obvious septicemia and urinary tract obstruction not limited to diabetes.

I am deeply grateful to Professor E. von Haam, Chairman of the Department of Pathology, for permitting the publication of this material.

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# Treatment of threatened premature labor with large doses of progesterone

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SINCE the dominant cause of death in the neonatal period is prematurity, attempts to reduce infant mortality must be directed above all toward a reduction of the frequency of premature delivery. A number of social, nutritional, and medical factors that contribute to premature deliveries are known,<sup>12</sup> and everything must be done, of course, to eliminate these factors. Unfortunately, though they may well be analyzed statistically, it is difficult to predict their influence upon the individual case. In clinical obstetrics, therefore, a substance capable of inhibiting uterine contractions is badly needed.

Encouraged by the work of Csapo<sup>2, 3</sup> who has carried out a long series of studies of the rabbit uterus from the molecular level to the uterus in situ, making it possible to formulate a theory on the hormonal control of myometrial function, we decided to carry out a clinical trial of progesterone in threatened premature labor. It seemed possible that one of the reasons for previous failures could be the use of too small doses, since it

has been realized only in the last few years that the turnover of progesterone is as high as 200 to 300 mg. or more per day at the end of pregnancy in the human. It was decided, therefore, to conduct a double-blind controlled study with fairly large doses of progesterone given parenterally.

## Material and methods

Approximately 150 patients with symptoms of threatened premature labor were treated during the 2 year period 1956-1957. If the symptoms subsided during treatment the patients were discharged from the hospital after varying periods of time. Some were delivered elsewhere and some were still undelivered at the time of this analysis. These cases have been excluded, leaving 126 cases for the present review.

The treatment with progesterone was started after a period of observation varying from one or 2 hours to 24 hours or more. Those patients in whom parturition seemed imminent were not treated. Patients with uneven admission numbers were treated with a preparation labeled Progesterone A and those with even numbers received Progesterone B. One preparation contained crystalline progesterone dissolved in vegetable oil with a concentration of 25 mg. per milliliter, and the other preparation was the same oil without progesterone. Not until the completion of the present analysis was the identity of the preparations disclosed to the staff, including the authors.

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Progesterone A contained inactive oil, while Progesterone B contained the active substance.

The dosage was 200 mg. daily for 3 days, 150 mg. for 2 days, and then 100 mg. per day. If the symptoms subsided, treatment was discontinued a week after their disappearance. Only 50 mg. was given on the last day.

The treatment caused no reactions that required its discontinuation. Some patients had tender infiltrations on the injection sites, and one patient in Group A and 2 in Group B did not want to continue for this or other reasons. It has been maintained that treatment with progesterone during pregnancy can cause virilization of female fetuses.<sup>9, 11</sup> In our study, virilization of neither infants nor mothers was observed.

The age distribution of the patients is shown in Table I and the obstetrical history in Table II. It is seen that 39 of the

patients had had one or more previous abortions, and 19 had had one or more premature deliveries.

Table. III Symptoms causing admission

Symptom	Series A	Series B
Hemorrhage from the vagina	28	23
Rupture of the membranes	19	21
Rhythmic or constant pains or backache	16	19

The number of patients having had episodes of bleeding and pains earlier in the present pregnancy was 10 in Group A and 23 in Group B. One patient in Group A and 4 in Group B had been treated with progesterone for such episodes.

The symptoms causing admission to the hospital for threatened premature labor are shown in Table III. The stage of pregnancy at the time of admission is shown in Table III, and the symptoms found on admission, in Table V. The interval between the onset of symptoms and the first injection of progesterone is seen in Table VI.

Table I. Age distribution

Age (years)	Series A	Series B
Under 20	14	5
20-29	36	43
30-39	12	14
Over 40	1	1
Total	63	63

Table II. Outcome of previous pregnancies

	Series A	Series B
<i>Previous abortions</i>		
No	45	42
One	16	16
Two	1	3
Three or more	1	2
<i>Previous deliveries</i>		
None	29	19
One premature	7	2
One premature and one term	3	0
One premature and two term	0	3
Two premature	0	1
Two premature and one term	0	1
Three or more premature	1	1
One term	15	23
Two term	5	7
Three or more term	3	6

Table IV. Stage of pregnancy on admission

Stage (month)	Series A	Series B
Fifth and sixth	7	11
Seventh	27	22
Eighth	25	28
Ninth	4	2

Table V. Symptoms found on admission

Symptoms	Series A	Series B
Hemorrhage from the vagina	23	15
Passage of amniotic fluid	18	23
Uterine contractions	27	24
No objective symptoms	4	11

Table VI. Interval between onset of symptoms and first injection of progesterone

Interval	Series A	Series B
Less than 12 hours	10	11
12-24 hours	15	22
24-48 hours	11	13
2-4 days	10	7
More than 4 days	17	10

If treatment was not interrupted by delivery it was continued for varying periods of time, depending on how long the symptoms were present. Table VII indicates the length of treatment in such cases, while the cases in which delivery took place during treatment are shown in the first half of Table VIII.

**Table VII.** Duration of treatment when not interrupted by delivery

Duration	Series A	Series B
Less than one week	4	1
8-14 days	28	21
15-21 days	2	8
22-28 days	2	1
More than 4 weeks	0	1

As seen from the tables, the two groups are in good agreement with regard to age distribution, obstetrical history, and symptoms. A statistical analysis with the use of the  $\chi^2$ -test<sup>7</sup> confirms that any difference between Group A and Group B is due to chance. The values of  $\chi^2$  are below the 5 per cent significance limit in all cases except in Table I and the second half of Table II, where the values fall between the 5 and 10 per cent limits. Group A comprises more patients under 20 years of age and more patients without previous deliveries than

Group B, but in most cases these patients are identical. It can therefore be concluded that the figures in Tables I-VII do not disagree with the assumption that the differences between the two groups are due to chance.

**Results**

Table VIII shows that there are no differences between the two groups with regard to results; the number of patients in whom delivery was successfully postponed was equal in both groups. A breakdown of the figures to show the relation to the initial symptoms—hemorrhage, rupture of the membranes, and pains—does not change the results.

To ascertain that the dominance of patients without previous deliveries in Group A does not invalidate this conclusion we have arranged the material in the following groups: (1) patients with no previous deliveries; (2) patients with only normal deliveries previously; (3) patients with premature deliveries previously. An evaluation of the results in these three groups in the same way as in Table VIII does not reveal any difference between Group A and Group B.

Placenta previa was found to be the cause of the symptoms of threatened premature labor in 5 patients in Group A and in 6 pa-

**Table VIII.** Time of delivery in relation to treatment, divided after the dominant initial symptoms

	Hemorrhage		Passage of amniotic fluid		Rhythmic or constant pains	
	Series A	Series B	Series A	Series B	Series A	Series B
<i>Delivery during treatment</i>						
First or second day	4	4	6	7	3	2
Third-seventh day	2	0	5	1	0	1
Eighth-fourteenth day	2	4	2	6	0	0
Fifteenth-twenty-eighth day	0	1	2	2	0	1
After twenty-eighth day	1	1	0	1	0	0
Total	9	10	15	17	3	4
<i>Delivery after treatment</i>						
During first week	2	3	0	1	1	0
During second week	2	2	0	0	1	0
Third or fourth week	3	1	0	0	4	3
After fourth week	12	7	4	3	7	12
Total	19	13	4	4	13	15

tients in Group B. Abruptio placentae occurred in 6 and 3 cases, respectively. In these cases the necessary obstetrical intervention, of course, determined the time of delivery.

The close agreement between the two groups is further illustrated by Table IX, which shows the birth weight of the infants.

**Table IX.** Weight distribution of infants

Weight (grams)	Series A	Series B
Less than 1,000	0	2
1,000-1,450	12*	7
1,500-1,950	10	11
2,000-2,450	13*	15
2,500-2,950	15	9
More than 3,000	13	19

\*Includes one stillborn infant.

### Comment

Haskins<sup>5</sup> found a decrease in the placental content of progesterone after the onset of labor, and Hoffmann and Uhde<sup>10</sup> found a reduction of the progesterone concentration in the blood of pregnant patients before and during labor. It has not yet been demonstrated, however, that a reduction of circulating progesterone occurs before the onset of premature labor.

Eichner and co-workers<sup>4, 5</sup> have had good results with large doses of progesterone in delaying the onset of labor after premature rupture of the membranes, but control material is lacking. Smith and Smith<sup>13, 14</sup> claim a general reduction of pregnancy complications with the prophylactic use of stilbestrol and progesterone. The fetal loss from prematurity was reduced, but the incidence of premature deliveries was not significantly lowered.

The present series is not large in view of the many factors that may cause premature delivery. Perhaps it should be further reduced by those cases in which delivery occurred during the first 48 hours after the beginning of treatment (13 cases in each group). It has been shown by Csapo,<sup>3</sup> in rabbits, that the effect of progesterone upon

the pregnant uterus has a latent period of 12 to 24 hours, and it is possible that the latent period is even longer in the human. Even after omission of these cases, however, the material is large enough to justify the conclusion that progesterone, even in large doses, is not the universal remedy in the prevention of premature delivery if symptoms are present. An inhibitive effect in a few cases cannot be excluded, however, and perhaps determination of the excretion of pregnanediol in the urine can disclose in which cases an effect is to be expected.<sup>1</sup>

Although the results are negative, we consider it justified to present the material since a similar double-blind controlled study with large doses of progesterone has not, to our knowledge, been carried out before.

In the rabbit, progesterone inhibits oxytocin-induced contractions, but, as mentioned, only after a certain latent period. The lack of effect in threatened premature labor in the human may have relation to this latent period, and experiments are therefore being carried out with the purpose of finding substances with a shorter latent period.<sup>6</sup>

A substance which can prevent premature delivery will greatly reduce the neonatal mortality. At the same time as we try to eliminate the known causes of premature delivery, the search for such substances must be intensified.

### Summary and conclusions

A double-blind controlled study of treatment of threatened premature labor with large doses of progesterone given intramuscularly has been presented. Sixty-three patients were treated with progesterone in oil in doses of 200 mg. daily initially, decreasing to 100 mg. daily as a maintenance dose. A similar number of patients were given inactive oil in the same quantities. The two groups were in good agreement with regard to age distribution, previous obstetrical history, and symptoms. The number of patients in whom delivery was successfully postponed was equal in the two groups.



We believe, therefore, that progesterone in the form presently used is unable to pre-

vent premature delivery once clinical symptoms are present.

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# Hourly variation in onset of labor and rupture of membranes

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OF THE theories concerning the initiation of labor, no single one gives an adequate explanation. In some instances it may be that more than one factor plays a role.

Variation in the frequency of onset of labor during each 24 hour period has been noted;<sup>1-3</sup> it was found that labor started in 62 per cent of a group of patients between 9 P.M. and 9 A.M.<sup>1, 2</sup> In an attempt to gain more insight into what starts labor, the time of its spontaneous onset and of prior rupture of the membranes in the Sloane Hospital for Women has been tabulated from March 1, 1958, through Feb. 28, 1959.

## Results

During the year, 4,154 patients went into labor spontaneously; in 3,313, or 79.75 per cent, labor began in the presence of intact membranes; in the remaining 841, or 20.25 per cent, the membranes ruptured spontaneously before labor. The distribution of all the patients according to the hour of onset of labor is shown in Table I and Fig. 1. The curve for the total number of patients shows a definite diurnal rhythm, with a maximum from 2 to 4 A.M. and a minimum between 11 A.M. and 1 P.M. The rhythmicity occurred every day in the year, irrespective of season, barometric pressure, humidity, or temperature. Between 9 P.M. and 9 A.M. 2,700, or 65 per cent, of the patients went spontaneously into labor.

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The curve for the hourly incidence of onset of labor in the 3,313 individuals with intact membranes is very similar to the preceding one. This curve also shows a definite diurnal rhythm, with a peak from 2 to 4 A.M. and a trough between 11 A.M. and 4 P.M.

The hour of spontaneous rupture of the membranes preceding onset of labor in the 841 women is given in Table I and Fig. 1.

Table I. Hour of onset of labor and of prior rupture of membranes

Hour	No. of patients		
	Rupture membranes before labor	Onset of labor, intact membranes	Onset of labor, total
12-1 P.M.	12	82	94
1-2	13	84	97
2-3	24	82	106
3-4	16	95	111
4-5	17	102	119
5-6	20	97	117
6-7	13	117	130
7-8	22	102	124
8-9	19	113	132
9-10	14	118	132
10-11	36	130	166
11-12	33	167	200
12-1 A.M.	47	174	221
1-2	74	157	231
2-3	82	222	304
3-4	69	219	288
4-5	79	223	302
5-6	55	188	243
6-7	45	193	238
7-8	57	133	190
8-9	35	150	185
9-10	22	143	165
10-11	20	143	163
11-12	17	79	96
Total	841	3,313	4,154

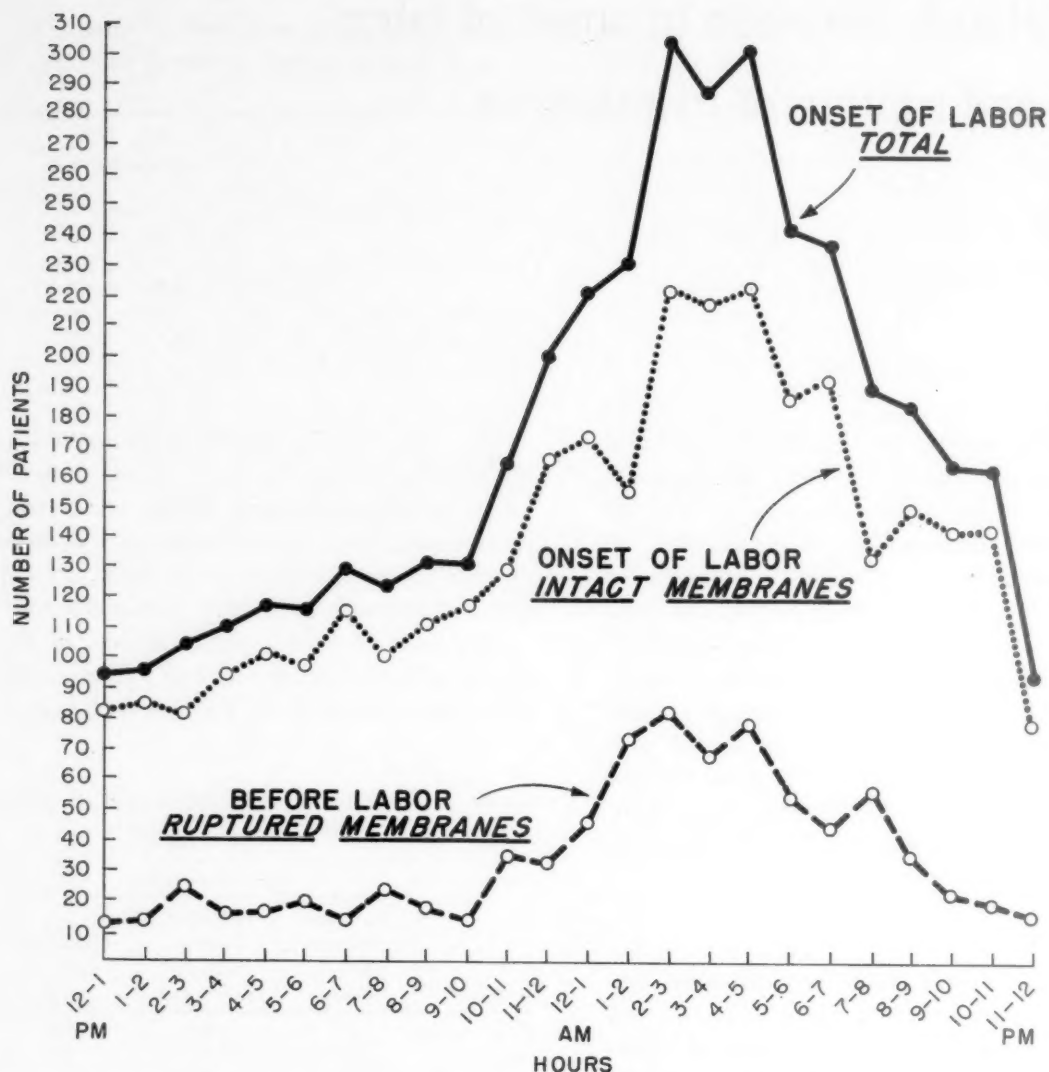


Fig. 1. Hourly incidence of spontaneous onset of labor in 4,154 patients and spontaneous rupture of the membranes before labor in 841 individuals. In 3,313 of the patients labor began in the presence of intact membranes.

These cases likewise showed a diurnal rhythm. The curves for onset of labor and spontaneous rupture of the membranes bear a close resemblance; however, the maximum and minimum frequencies of membrane rupture are spread over wider periods of time. The hourly variation in incidence is even more marked than with respect to onset of labor. The membranes ruptured spontaneously in 626 of the 841 patients, or 74.43 per cent, between 9 P.M. and 9 A.M.

These data have been analyzed statistically by the chi square method. When checked per 12 hour period (9 P.M.-9 A.M.; 9 A.M.-

9 P.M.) and per hour, the probability of the frequency distributions in the respective curves being due to chance is  $P \ll 0.001$ .

#### Comment

That the membranes ruptured in only one fifth of the patients before labor began and that they usually do not rupture until after complete dilatation of the cervix is perhaps fortunate as an aid in maintaining asepsis in utero and in providing for the bag of waters with its hydrostatic pressure against the cervix and lower uterine segment. It has been shown that during early labor the

membranes become loosened from the lower uterine segment, after which they slip back and forth over the underlying mucosa.<sup>4</sup> This loosening of the membranes permits their being stretched more uniformly over a greater area. Consequently, the likelihood of their remaining intact is increased.

The graphic similarity in the diurnal rhythmicity in the hour of onset of labor and rupture of the membranes might suggest a common cause for both phenomena. The maxima of the frequency distribution curves show that labor usually starts and the membranes rupture most often when patients are at rest, if not actually asleep. It appears possible that, as with stripping or artificial rupture of the membranes, rest and sleep relaxation permits descent of the pre-

senting part with stretching of the lower uterine segment and pressure on the surrounding nerve ganglia, with consequent initiation of labor. The increased incidence of spontaneous rupture of the membranes during rest and sleep could be accounted for on the same basis.

#### Summary

The frequency distribution curves for spontaneous onset of labor and spontaneous rupture of the membranes before labor reveal a definite diurnal rhythmicity during each 24 hour period. Patients most often commence labor and rupture the membranes preceding labor during the hours of rest and sleep.

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# Single application of intravenous Pitocin for induction of labor in toxemias of pregnancy

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WHEN termination of pregnancy complicated by toxemia is considered necessary, repeated stimulation of the uterus with intramuscular or intravenous Pitocin on successive days has been found to convert a long, firm cervix into one displaying effacement and dilatation and to result in eventual expulsion of the fetus.<sup>1-7</sup> It is generally felt that eclamptic women readily deliver following Pitocin stimulation.<sup>8</sup> However, spontaneous labor commonly develops during eclampsia regardless of the period of gestation or the cervical status.

Eastman,<sup>9, 10</sup> in editorial comments relative to fulminating toxemias, has stated that intravenous Pitocin is not the solution for overcoming a long, closed cervix when the head is floating because "it just doesn't work under these circumstances." He does not approve of repeated administration of Pitocin intravenously for several successive days and feels it is not sufficiently dependable to warrant its use if prompt delivery is urgently indicated.

Fulsher<sup>11</sup> reported 5 cases in which each patient delivered following a single infusion of Pitocin. In 4 of them, the cervix was

uneffaced and undilated, and the presenting head was unengaged.

The purpose of this paper is to appraise in a series larger than heretofore reported in the literature the value of a single administration of intravenous Pitocin. This method was utilized despite the presence of a long, closed cervix and unengaged presenting part in cases of nonresponding toxemia where the decision had been made to terminate the pregnancy. Failure of this procedure was followed by abdominal delivery.

Our approach was based on a knowledge of physiologic principles, with the realization that the lower uterine segment and cervix must go through a preparatory stage before true labor begins. This preparatory stage entails (1) unfolding of the lower uterine segment, resulting in descent of the presenting part and (2) effacement of the cervix. Following this, true labor begins as evidenced by progressive dilatation of the cervix. Active labor was regarded as beginning when contractions occurred at intervals of 3 minutes or less, of 45 to 60 seconds' duration, accompanied by palpatory evidence of the strength of the contraction. The contractions were accepted as of good quality when the uterus was not indentable, or just barely so. We considered the case as a Pitocin failure if the uterus failed to respond when subjected to a maximum concentration of 3 ampules per 1,000 c.c. of fluid introduced at a rate which exceeded 80 drops per minute or if satisfactory results were not obtained within 8 to 12 hours of the above regimen. Amni-

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otomy was practiced when the presenting part had entered the pelvis and the cervix was effaced and 2 to 3 cm. dilated.

**Method**

A double setup with Y tubing, where one bottle contains the Pitocin, is preferable, but as an alternative the Pitocin can be added to the fluid of a single setup after the flow has been started and regulated. Both techniques obviate the risk of introducing an excessive initial dose.

One ampule of Pitocin per 1,000 c.c. of 5 per cent dextrose in water was used initially. The rate of flow was begun at approximately 15 drops per minute and was gradually increased according to the uterine response. When the rate of flow exceeded 80 drops per minute, the bottle was replaced with one containing 2 ampules of Pitocin, accompanied by a comparable reduction in the rate of flow. The maximum amount of Pitocin added to 1,000 c.c. of fluid was 3 ampules. By this procedure of increasing the concentration of Pitocin and decreasing the rate of flow, overhydration of the patient is prevented. It is important to note that an obstetrical resident was constantly in attendance while the patient was receiving the Pitocin.

**Material**

Fifty cases of nonresponding toxemia, consisting of either pre-eclampsia or pre-eclampsia superimposed on hypertensive renal vascular disease, were utilized. These represent a group of cases which were available to the junior author while on the obstetrical

service at Cook County Hospital under supervision of the attending staff agreeable to this regimen. At Cook County Hospital the majority of nonresponding toxemias, especially when the presenting part is floating and the cervix is uneffaced and closed, are terminated by cesarean section. Less urgent cases may be managed by one of several methods: induction by amniotomy with or without the use of Pitocin, repeated Pitocin stimulation, or cesarean section, depending on the features of the individual case and upon the attending personnel.

Of the 50 patients, 23 were primiparas, 11 of whom were less than 40 weeks pregnant and 12 of whom were at or near term. Of the 27 multiparas, 13 were preterm and 14 were at or near term. In all cases, the cervix was not considered "ripe" on vaginal examination, and the presenting part was unengaged. The primiparous cervixes were long and closed; the majority of multiparous cervixes were somewhat patulous, but the internal os was closed. Pelvic adequacy was determined by internal digital evaluation. Delivery was effected under pudendal block or local anesthesia. Low forceps and episiotomy were used when necessary. On each of 2 occasions a midforceps Kielland rotation was required to facilitate delivery.

**Results**

Of the 50 patients, 45 were successfully delivered vaginally (Table I). The 5 failures will be examined individually. Twenty of the 45 were primiparas (9 preterm, 11 at term). The average duration of Pitocin stimulation for primiparas was 7 hours and

**Table I.** Data regarding the 45 patients who were delivered vaginally with Pitocin stimulation

	No. of cases	Birth weight			Duration of Pitocin stimulation		
		Average	Smallest	Largest	Average	Shortest	Longest
Primiparas							
Preterm	9	4 lb., ¾ oz.	2 lb., 12 oz.	5 lb., 4 oz.	7 hr., 46 min.	3 hr., 45 min.	14 hr., 30 min.
Term	11	7 lb., 7 oz.	5 lb., 12 oz.	8 lb., 9¾ oz.	8 hr., 36 min.	6 hr.	18 hr., 50 min.
Multiparas							
Preterm	12	4 lb., 1¼ oz.	2 lb., 10 oz.	5 lb., 6½ oz.	6 hr., 41 min.	2 hr., 5 min.	10 hr., 45 min.
Term	13	7 lb., 8 oz.	5 lb., 15 oz.	8 lb., 15 oz.	5 hr., 13 min.	40 min.	14 hr., 30 min.

46 minutes for the preterm patients and 8 hours and 36 minutes for the term patients. Similarly, with the multiparas it required 6 hours and 41 minutes for the preterm patients and 5 hours and 13 minutes for the term patients. The longest period of Pitocin administration needed to effect delivery was 18 hours and 50 minutes in a primipara at term, and the shortest was 40 minutes in a multipara at term.

It is important to stress the following

factors relative to the amount of Pitocin actually required to effect delivery. Only one ampule per 1,000 c.c. of 5 per cent glucose in water was used in all but 2 of the patients who were delivered vaginally. Also, the majority of patients responded to a rate of flow between 40 and 60 drops per minute, some to lesser rates and a few, particularly the primiparas, to rates between 60 and 80 drops per minute. Massive doses were not generally employed or needed. If

**Table II.** Data regarding the 5 cases considered Pitocin failures (all cesarean sections)

Case	Gra- vidity	Par- ity	Duration of gestation (weeks)	Bag of waters	Duration of pains (hours)	Amount of Pitocin	Maximum cervical dilatation	Oper- ative findings	Fetal outcome	Post- mortem findings of baby
1	i	0	36	Ruptured before ad- mission	24 (irregu- lar)	3 am- pules in 24 hr.	2-3 cm.; no change	----	5 lb., 3 oz.; lived 24 hours	Broncho- pneumo- nia and atelecta- sis
2	i	0	35	Intact	36	3 am- pules	No change; 2-3 cm.	----	4 lb., 8 oz.; survived	----
3	i	0	39	Artificial rupture after 20 hours	30	2 am- pules	3-4 cm.; no change	Constric- tion ring	6 lb., 1 oz.; survived	----
4	vi	0	34	Ruptured on admission	28	3 am- pules	2-3 cm.; no change	----	4 lb.; sur- vived	----
5	iii	ii	37	Ruptured on admission	40	2 am- pules	5 cm.	Constric- tion ring	5 lb., 13 oz.; sur- vived	----

**Table III.** Perinatal mortality

Case	Time of death	Weight of baby	Duration of labor (hours)	Mode of delivery	Maternal complications	Remarks
1	Ante partum	2 lb., 10 oz. (macerated)	7	Vaginally	Diabetes and toxemia	Dead prior to in- duction
2	Ante partum	3 lb., 4 oz. (macerated)	2	Vaginally		Dead prior to in- duction
3	Intrapartum	2 lb., 10 oz.	9	Vaginally; breech	Obesity (250 lb.)	Death attributable to Pitocin in- duction
4	6 days post partum	2 lb., 11 oz.	8	Vaginally		
5	1 day post partum	5 lb., 13 oz.	24	Cesarean section	Constriction ring	

an adequate response was not obtained with one ampule per 1,000 c.c. of fluid administered at a maximum rate of 80 drops per minute, it was not usually obtained with larger doses.

Descent, cervical effacement, and dilatation were best observed in the primiparous patients who were exposed to frequent vaginal examinations at intervals of one-half to one hour. Descent of the presenting part, progressive softening, and effacement occurred prior to dilatation, the process varying from  $2\frac{1}{2}$  to 8 hours in duration. The process of cervical dilatation required from 2 hours and 30 minutes to 10 hours and 50 minutes. There was no distinct time correlation between the 2 processes of effacement and dilatation. In some cases, effacement consumed more time than dilatation, and the reverse also occurred. The rate at which descent of the presenting part, softening, and effacement of the cervix occurred, therefore, was no index as to the subsequent rate of dilatation, both processes being completely variable. Table II summarizes 5 cases considered Pitocin failures.

In essence, only one death is attributable to the procedure of Pitocin induction. This involved a 2 pound, 10 ounce infant with breech presentation (Table III).

### Complications

**Constriction ring.** We have to assume that in both instances these resulted from the Pitocin procedure. It is doubtful that they were present prior to induction since labor progressed so well in the early phases.

**Blood pressure elevations.** Minor fluctuations of the systolic pressure to 20 mm. Hg and 10 mm. Hg of the diastolic pressure frequently occurred. However, there were no sudden rises or drastic alterations that necessitated discontinuing the procedure.

**Fetal distress.** This was evidenced by fetal heart tones falling to and remaining below 100 per minute, and meconium in cephalic presentation. There were some minor variations during contractions, but they returned to normal during the relaxation phase.

**Fetal asphyxia at birth.** Two fetuses re-

quired tracheal catheter and oxygen for less than 2 minutes. All others breathed and cried spontaneously with simple stimulating measures plus Nalline.

**Trauma to the birth canal.** The vagina and cervix were visually examined in all cases. One cervical laceration was found and was repaired with 2 interrupted sutures.

**Postpartum hemorrhage.** This was avoided by continuation of the Pitocin drip for several hours following delivery.

### Comment

This series, even though relatively small, serves to emphasize several important points with regard to Pitocin induction where conditions may not seem to lend themselves to this procedure. Pitocin responsiveness varies not only from patient to patient, but also within the same patient during the course of an induction. Some uteri, once good contractions have become established, become more sensitive and less is required to promulgate the contractions. Other uteri may develop an apparent tolerance to Pitocin and become refractory to it, thus requiring an increasing dosage to maintain good uterine action. Therefore, trepidation in transgressing "safe bounds" and confining the rate of administration to predetermined set levels is likely to terminate in failure. Page<sup>12</sup> clearly indicated this in explicit terms worthy of direct quotation: "The threshold of sensitivity parallels the degree of spontaneous motility, and may vary 100 fold from one patient to the next. There is, therefore, no standard dose, no safe dose, and no dangerous dose of Pitocin when measured in minims, milliliters or units. In accordance with the principles of a bio-assay, dosage can only be measured in terms of uterine response."

In primiparous patients, prior to dilatation, the unripe cervix undergoes softening and effacement which is often preceded by the unfolding of the lower uterine segment and descent of the presenting part. The latter processes usually require a generous amount of time,  $2\frac{1}{2}$  to 8 hours, an interval during which many people become dis-



couraged and concede a Pitocin failure too soon.

In reference to the quality of uterine contractions, it is not sufficient merely to produce a generalized "tightening" of the uterus comparable to a Braxton Hicks contraction. This is a passive state as compared to an active working contraction exerting a downward expulsive force. The two can be differentiated by the patient's reaction (increasing pelvic discomfort in the latter) and by the tension exerted on the lower uterine segment adjacent to the internal cervical os as determined by vaginal examination.

There is more unity of opinion<sup>13, 14</sup> relative to the ability of the pregnant patient's serum at term to inactivate the vasopressin factor elaborated by the posterior lobe of the neurohypophysis, than the oxytocic principle. Dicker and Tyler<sup>14</sup> found that up to the end of the seventh month, normal pregnancy is protected against any abnormal elaboration of oxytocin by the enzyme pitocinase. Then, after the thirtieth week, the oxytocic inactivating power disappears and there is nothing to interfere with the physiologic action of oxytocin on the gravid uterus. These findings are in opposition to those of Page,<sup>15</sup> who determined a progressive elevation of pitocinase activity from the fourth to the thirty-eighth week after conception, the high level being maintained during labor and disappearing rapidly after delivery. Dicker and Tyler's findings would be more compatible in furnishing a reason

as to why Pitocin induction any time after the seventh month of gestation is practicable and successful anent the presence of an unfavorable cervix and a floating presenting part.

If we can assume the above correlation, then we can question whether cervical status is a valid criterion when induction of labor is considered. Is it essential for a cervix to be ripe before labor can ensue, or is it a matter of promoting adequate corpus action to overcome the cervix regardless of its condition? It is an obstetrical enigma that in premature labor usually the adverse conditions of long cervix and floating presenting part are readily overcome by nature despite the efforts on the part of the obstetrician armed with many drugs to quiet uterine activity.

### Summary and conclusions

1. Fifty patients with nonresponding toxemia of pregnancy exhibiting floating presenting parts and uneffaced closed cervixes were subjected to intravenous Pitocin stimulation, as a single application. Forty-five were successfully delivered vaginally; 20 were primiparas, 25 were multiparas.

2. Pitocin administration was gauged solely on the basis of uterine response, the actual dosage being of secondary consideration.

3. Careful administration of Pitocin to toxemic patients considered unfavorable for vaginal delivery merits trial, in a manner such as that described, prior to the termination of the pregnancy by cesarean section.

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### Discussion

DR. PHILIP J. STEIN, Chicago, Illinois. In their study of several years ago, Tamis and Shey<sup>1</sup> pointed out that "the elective induction of labor by intravenous Pitocin can be accomplished on any patient at or near term regardless of the ripeness of the cervix." Drs. Fields and Varga have by this study in a great measure shown that this is true.

Tamis and Shey came to their conclusion after using Pitocin for induction of labor in patients with toxemia in the multiple application technique, much as has been employed at the Cook County Hospital. Except for this study by Drs. Fields and Varga, the "unripe" cervixes of patients at the Cook County Hospital who required termination of pregnancy have been "ripened" by the daily intravenous infusion of a 1:1,000 solution of Pitocin. In this manner, effacement takes place more slowly, usually in a period of 2 or 3 days, more nearly simulating the manner in which it occurs normally, where the process has been observed to take place over a period of days or weeks.

While there is no doubt that effacement, dilatation, and delivery can be accomplished in a "single sitting," so to speak, it would seem more physiologic and possibly less potentially traumatic to mother and fetus to grant a longer span of time for these processes to be effected, when delivery is not emergently imperative. Pituitary extract has had such a bad name since its introduction in obstetrics early in the century that many of us have been prejudiced against its use or have been reluctant to use it more widely. I remember quite clearly the great courage that was required to proceed with a study of the treatment of uterine inertia by intermittent intramuscular injections of dilute Pitocin inaugurated by Dr. Daro at the Cook County Hospital only 14 years ago. Great progress has been made since then.

It is because of this progress and the great boon that oxytocics, properly used, have proved to obstetrics that we should proceed with their use in as physiologic a manner as we can. Nevertheless, we are greatly indebted to Drs. Fields and Varga who have shown what can be accomplished when the demand is present. Certainly it has been shown that vaginal delivery is the route of choice for these patients who may have a nonrecurring disease and for granting a better fetal survival rate. It is, therefore, comforting to know that, when it is necessary to

empty the uterus more rapidly, this route is not closed to the obstetrician because of an uneffaced closed cervix and an undescended presenting part. Certainly a success rate of 90 per cent and an average labor of 8 to 8½ hours are to be reckoned with. Even if one should discount some of the success achieved with the multiparous patients at term, the results are still satisfactory. In this study, the authors have confirmed the findings of Dr. Caldeyro-Barcia who presented his studies to this Society only last year.

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DR. HARVEY A. GOLLIN, Chicago, Illinois. Most of us are fortunate in our private practice in infrequently having the opportunity of treating severe pre-eclampsia. This is not true at institutions such as the Cook County Hospital where the patients frequently have no prenatal care or inadequate prenatal care and are admitted to the hospital in a serious phase of this complication of pregnancy.

Although there have been new ideas as to therapy of this disease, most obstetricians still feel that delivery is the most successful therapy. Drs. Fields and Varga present excellent statistics on a method for such delivery.

Induction of labor in the presence of a "ripe" cervix and a "not so ripe" cervix has been quite successful. Induction of labor in the presence of an uneffaced cervix has not been given a chance because we did not consider the chance for successful induction to be sufficient.

In reviewing the method of induction presented, I find that the difference in the usual mode of induction as compared to that of Drs. Fields and Varga is the degree of stimulation used. They produced strong uterine contractions which were of 45 to 60 seconds' duration. This difference can best be emphasized by the fact that repeated administration of Pitocin solutions on successive days with the production of 30 to 40 second contractions have frequently failed to induce labor, particularly in the presence of intact membranes. Certainly, the production of contractions as indicated by the essayists would require firm indication for induction, a most careful selection of patients and constant surveillance by a trained person during this period of stimulation.

The presence of 2 constriction rings is higher than would be expected in a comparable number of inductions with more favorable cervixes. I would like to ask Dr. Fields whether he has an explanation for this high incidence.

It is difficult to present closely comparable statistics to the unusual conditions presented this evening. I have, in my studies of the use of Pitocin inductions in the management of premature separation of the normally planted placenta at the Cook County Hospital in the past 7 years (1951-1957), found 23 instances in which the cervix was long at the time of induction but sufficiently open in most instances to allow artificial rupture of membranes before the administration of dilute intravenous Pitocin.

There were 5 failures in this group. Four of these should be discounted because of inadequate trial due to great caution of administration in the presence of grand multiparity. The failure was in a para iii with a 24 weeks' gestation, a long closed cervix, and intact membranes. The

longest labor was 10 hours and the shortest 50 minutes.

The incidence of successful induction in this series was very satisfactory in the presence of a so-called "unripe cervix" and the length of labor surprisingly short in some instances, as has been noted in the paper presented this evening.

DR. FIELDS (Closing). When one acts on the premise that cesarean section carries with it a potential mortality that is tremendously higher than vaginal delivery, then one can also feel that when there is an indication for terminating the pregnancy, an attempt should be made to deliver the parturient vaginally, regardless of the status of the cervix, unless other conditions rule out the vaginal route.

As to the question of constriction ring, some years ago we presented a paper on constriction ring dystocia. We mentioned the possibility of increasing the incidence of constriction rings by the use of Pitocin. This seems to have occurred in our series.

## CURRENT OPINION

### Pertinent Comments

# The relation of nasopharyngeal infection to infertility

BERNARD SANDLER, M.D., D.M.R., D.R.C.O.G.

*Manchester, England*

THE idea that there may be a nasogenital relationship is not new and, indeed, dates from antiquity. The phenomenon of vicarious menstruation appearing as epistaxis is well recognized as a clinical phenomenon.

This relationship is obviously atavistic, for among animals the nose plays an important part in the sexual relationship. In Belfast, Morton<sup>8</sup> has shown that when the olfactory apparatus is damaged, the animal loses sexual interest, and copulation ceases. The obvious relationship between sex and the nasal function in animals has its counterpart in man where sex stimulation is associated with certain olfactory perceptions.

The first reference in the literature is by Buchan,<sup>2</sup> in 1769, who states "If the genitals be immersed for some time in cold water it will generally stop a bleeding of the nose" and goes on to say "I have seldom known this to fail!" A scientific basis for this has been shown by Spiesman,<sup>10</sup> who noted that the application of a cold stimulus to a portion of the skin caused a lowering

of the tonus of the nasal mucous membrane with vasoconstriction—hence the mechanism of the use of a cold key down the back in the treatment of epistaxis. Bresgen,<sup>1</sup> in 1881, observed congestion of the nasal mucous membrane during menstruation, but it was Mackenzie,<sup>5</sup> in 1884, who gave the first accurate observations, and who concluded that there is "an intimate physiological association between the nasal and the reproductive apparatus." This is probably a reflex action and he seems to have been thinking in terms of a nervous mechanism when he said that "the irritation of the one reacts upon the circulation and possibly nutrition of the other." Fliess<sup>3</sup> some years later reported changes in the nose during menstruation, pregnancy, labor, and the puerperium. He described a local hyperemia and increased sensitivity in the "genital spots," as he called them, of the middle and lower turbinate areas.

Most of the nineteenth-century literature has been concerned with the relation of epistaxis to the various aspects of sex function, and by 1912 Seifert<sup>9</sup> was able to quote 296 references to this aspect of the problem.

He (1) concluded that there is an ana-

*From the Manchester Jewish Hospital.*

*Presented before a meeting of the Society for the Study of Fertility, London, 1958.*



tomical and physiological correspondence between the sex organs and parts of the nose and that there is a nervous pathway between them but the nature of it is not known; (2) postulated a nasal reflex neurosis, and (3) rejected the theory elaborated by Fliess that there is such a thing as a nasal cause of dysmenorrhea.

It was not until 1936, however, that Mortimer, Wright, and Collip<sup>6,7</sup> showed that in the monkey the mucous membrane of the turbinates responds specifically to estrogenic hormone and that the application of estrogen produces redness and swelling similar to the changes known to occur in the physiological processes of menstruation and pregnancy. Moreover, they were able to reproduce these effects in castrates, and they showed that the graph of nasal changes corresponded closely with the excretion of estrogen in pregnancy.

In atrophic rhinitis they were able to show (and for some years the treatment became quite popular) that the nasal mucosa will respond effectively to the application of estrogen in oil. However, all this early work seems to have been more concerned with the effects on the nasal mucosa of sexual changes in the rest of the body. More recently, Holmes, Goodell, Wolf, and Wolff<sup>4</sup> have shown that stress alone can produce changes in the nose which may vary from a simple hyperemia to either a rhinorrhea or even the formation of a true sinusitis with pus. These observations were made by different observers including a psychiatrist and a rhinologist who observed the same patient but did not know what the other's findings were until the end of the experiment. They showed a very close correlation between the stress situation and nasal symptoms.

Although Mackenzie and associates were the first to describe what was thought to be a reciprocal nasogenital relationship, very little if any work appears to have been done on the possible effects of the nose on the genital organs.

My attention was drawn to this aspect of the matter some years ago when I was

confronted with a case in which a non-receptive cervical mucus had remained hostile to spermatozoa of many different donors over a very long period. The patient was a woman, aged 36, with a history of 3 years of sterility. She had already had a great deal of investigation before she came under my care. I found that she had a profuse growth of a mixture of *Escherichia coli*, *Bacillus proteus*, and *Staphylococcus pyogenes* in her cervix. She was treated vigorously for this condition, and eventually her cervical mucus became sterile but was still nonreceptive to spermatozoa. One day I heard her sniffing a great deal and this drew my attention to the fact that she might have a sinus infection. Indeed she complained of continuous stuffiness of the nose but, as I have discovered with many other patients since, it is not a condition about which they volunteer any information nor does it seem to cause them a great deal of distress in the way of physical symptoms. X-ray examination showed both sinuses obscured, and lavage produced a good deal of pus from both antra; *E. coli* was recovered from the pus. This patient conceived the next month without any treatment other than the lavage. Since then, I have been searching for similar cases and have found about 24. In order to give some sense of perspective, however, it should be said at once that these 24 have been found in a consecutive series of over 500 cases; the incidence is, therefore, quite small and no attempt whatever is made to draw any kind of statistical conclusions as to the frequency with which nasopharyngeal infections are a factor in sterility. My purpose is merely to draw attention to the fact that they can be and that in the occasional case it is worth searching for.

On close examination of the 24 cases I have been able to accept only 16 women in whom, in my view, there is an undoubted clear association between the removal of nasopharyngeal sepsis and the onset of pregnancy. In the other cases, although I am sure such sepsis may have had an important bearing on the case, nevertheless, there were

other factors present which obscured the issue, and I felt it better to exclude them from this series. It will be noted\* that in all this series the postcoital tests, with one exception, have remained negative despite standard methods of treatment over a period varying from 6 months to 2½ years. Such treatment has included cauterization, the use of antibiotics, local use of antiseptics, short-wave diathermy, and other methods. It can be said of all these cases that the possibility that the pregnancy is fortuitous and might have occurred without treatment is rather unlikely in view of the length and type of treatment which all these patients had undergone. In effect, each patient has had to serve as her own control.

The success in these cases drew my attention to the possibility of male infertility responding to the treatment of nasopharyngeal infection. A number of such cases are under active investigation and already two pregnancies have been achieved which seem to be attributable entirely to the improvement in semen quality which has followed the

treatment of the husband's sepsis. In both cases the antra were infected. In one *E. coli* and in the other *Staph. pyogenes* were recovered in the washings. The treatment of the nose has immediately been followed by an increase in sperm density and improvement in sperm viability with diminution in the number of abnormal sperm cells, and corresponding improvement in sperm motility has also occurred. The number of cases is insufficient to report at this stage but it would seem worthwhile investigating the possibility of this type of focal infection in severe infertility.

As these few cases represent the results of some 500 consecutive couples investigated at this clinic, it is not suggested that this is a condition of frequent occurrence. Nor does this paper lay claim to provide any kind of statistical significance. It is felt, however, that the intractable case of infertility in which the cervical mucus remains hostile to sperm invasion, no matter what local treatment is given, may well respond to the eradication of nasopharyngeal sepsis when this is present.

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\*A table detailing this may be obtained from the author.

# Mancinism

ALLAN C. BARNES, M.D.

Cleveland, Ohio

THE recent paper by Ingalls and Purdy in the *New England Journal of Medicine* on congenital anomalies served, among other things, to rekindle our own interest in the least conspicuous of the congenital anomalies—left-handedness. The official dictionary term is “mancinism,” and clearly indicates its status: a mancunist in ancient Greek times was a deformed or crippled person not infrequently put to death in the neonatal period by exposure to the elements on a mountain top. This broad but morbid term remains with us today as the official name for the commonest of congenital anomalies.

My study consisted simply of a series of interviews on the subject. Seeking out those who should know, I gathered certain authoritative information. In view of the well-known fact that there are no left-handed violinists in symphony orchestras, we started with the violin teacher. Here-with are the interviews (together with our comments) to date:

**Violin teacher.** Oh, yes, we always put the bow in the youngster's right hand . . . bowing is so important, you know. If he is left-handed? Why, I put the bow in his right hand . . . yes, I can see that, but the fingering is so important, you know. I tell them it's almost an advantage to be left-handed. No, that doesn't mean it's a disadvantage to be right-handed. It's just an advantage. To be handed, I mean.

**Comment.** This Society may well go down in history as the civilization which thought it worth while to manufacture left-handed golf clubs (costing perhaps \$225) but not left-handed violins. Since the violin is a

symmetrical instrument, all it would require would be to put the strings on the bridge in the opposite order and to manufacture a left-handed chin piece (costing perhaps \$2.00).

**Sociologist.** The contemporary studies are interesting because they show left-handedness is definitely on the increase. The St. Louis survey in 1915 indicated 2.9 per cent of the group was left-handed. Chamberlain's paper in 1928 gave the figure of 4.3 per cent. Rife, in 1940, reported that 7.45 per cent of the group studied were left-handed. Always the men exceed the women. Always there are more than in the last study.

**Comment.** These studies are good. Not just asking grandmother how many of her grandchildren are right- or left-handed, but mass surveys with pencil tests, catching, throwing, and generally playing second base with the interviewer. This confuses the hereditary pattern. If it were a recessive it would disappear. But if it were a clear-cut dominant wouldn't it increase faster? Probably a dominant recessive. Or a recessive type of dominant.

**Geneticist.** Handedness is variously reported by the authorities. In Sinnott, Dunn, and Dobzhansky, it appears in a pedigree with left-handedness as a simple dominant. More recently Tanner has summarized it lucidly as follows: “Handedness is probably in the main a hereditary character; that is to say, heredity determines some neurological difference which predisposes the individual to use preferentially his left or right hand. Despite a considerable volume of work on this subject, however, the nature of the neurological difference is not yet understood. Handedness is certainly a



graded character, not an absolute one; indeed, when a test is given allowing complete quantitation of "handedness" the scores are distributed quite unimodally, with no indication of a break between left-handedness and right-handedness at all. . . . In these circumstances it is not surprising that the genetics of handedness is confused and likely to remain so until its physiological basis is better understood.

*Comment.* The contemporary geneticists are an alert group and one must admire them tremendously. They have delineated a clear-cut science, and they aren't easily stampeded. In this instance, however, one most admires the obvious ability to sit on a fence neatly. Professor Tanner is lucid enough, and we imagine that right at the moment our own investigation is contributing mightily to clearing up the confusion he mentions.

*Psychologist.* I should think the answer would be obvious. The reason that the current surveys show left-handedness is on the increase is that we don't make any effort to change the children. The old-fashioned schoolteacher was literally barbaric! Nowadays we are much more enlightened about this problem. As a result there is less stammering and stuttering, too, . . . no conflicts.

*Comment.* This is the official stand of the psychologist of today: "We don't try to change the children." Nonsense! All we do to the children is to precipitate them into a completely right-handed civilization. Every pencil sharpener is built for right-handed people . . . every can opener. All scissors are right-handed. No conflict indeed! We will believe that when 7.45 per cent of the gearshift handles stick out on the left side of the steering-wheel shaft.

*Classicist.* It wasn't always thus. There is evidence that some of the old Semitic tribes were completely left-handed. And their writing went from right to left. The Greeks were originally an ambidextrous nation, and their writing was of the boustrophedon type (literally translated: "like the plowing of the ox"). They started the first line in the upper right-hand corner

and went to the left; then the second line went from left to right; and the third line from right to left, etc. A very logical way to write, and an easy way to read, I must say. Hereditary? I wonder. There must have been a strong environmental *Zeitgeist*. The chief factor which changed the Greeks was the invention of the military phalanx. It became necessary for every man to hold his shield on his left arm and his spear in his right hand. They simply changed an ambidextrous nation to a right-handed nation. Had to change, or die. Their writing changed at the same time to the left-to-right line.

*Comment.* The phalanx was introduced from the Macedonians, but we don't know how they wrote. Possibly like the plowing of an ox (boustrophedon to you). The Babylonians and Assyrians wrote from left to right, but we don't know how they plowed. Between the years 100 B.C. and A.D. 100, a Jew who was writing in Hebrew would write from right to left. If he were writing in Greek (the international language of the day) he would write from left to right. There is no reliable information on their right- or left-handedness, but certainly they must have been talented.

*The President of the United States.* That principle from the Greek army still persists. I'd like to see you train an infantry division which was part right-handed and part left-handed. When they start we don't care what they are. But when they finish everyone has to shoulder arms on the same side. Every sniper and every infantryman is trained to put his gun along the right-hand side of a tree, regardless of what hand he prefers.

*Comment.* This brings us back to the orchestra. Uniformity is the key to safety when there are 65 people crowded on stage and all bowing like mad. Who wants to be stabbed? It's the phalanx principle. If the violin is the shield, and the bow is the spear, then they must all be held the same way. Hold them the same way, or die!

*Elderly obstetrician.* It may not be hereditary at all, but a congenital trait based on



some intrauterine accommodation. Just set the placenta in a pan and hold up the cord. If the spirals are around to the right, the baby will be right-handed. If around to the left, the baby will be left-handed. Shows the way the baby has been turning.

*Comment.* If looking this up in Ramsbotham's *System of Obstetrics*, look under "Conditions of the Funis." "Funis" is a lovely term (compared with our abrupt word "cord") which is disappearing from modern speech. Ramsbotham is an 1855 text bound in leather. Leather is a lovely binding (compared to our rough cloth-board) which is disappearing from modern libraries.

**Marine biologist.** The percentage of right-handedness and left-handedness in lobsters is the same as in men. When served a lobster, always note the differential size of the right versus the left claw (this applies to

pincer and crusher). Also note whether you are eating a male or a female. Record the data, and you will find that it matches the statistics cited above for human beings.

*Comment.* This is hard on the Funis theory since lobsters have no umbilical cord. The lobster conceptus (we are not certain about that terminology) voluntarily fastens to the bottom of the mother's carapace for a while, proving that the conceptus can recognize its own mother (much less a male versus a female lobster) much faster than can we.

**Senior night supervisor.** Just clear out the babies' throat, wrap them in a blanket to keep them warm, but leave their hands free. After you get out the suture material for the episiotomy, go back and look. The left-handed ones will have their left thumbs in their mouths; the right-handed ones the right thumbs. That's all there is to it.

*Comment.* Yes, Ma'am.

## Editorial

### The new format

WITH this number, that of January, 1960, the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY appears in a new format. We believe this represents many improvements which will appeal to both contributor and reader.

The page size is moderately increased from the old dimension of  $6\frac{7}{8}$  by 10 to  $7\frac{1}{4}$  by  $10\frac{1}{2}$  inches, producing an increased page surface of nearly 10 per cent. Following the present trend believed to aid in ease and rapidity of reading, the text will be set in two columns instead of running across the entire page.

The style of type is changed from the somewhat old-fashioned DeVinne to the classic well-received Baskerville. In the terms of the professional, the major portion of the text will be set in 10 point type leaded 2 points. Case histories and other portions of the text will be set in 9 point, leaded 2 points. Formerly, this material was set in 10 point solid and in 8 point, and we believe

that these changes will contribute to greater legibility.

Within a few months there will also be a change in the method of binding to the so-called "perfect" technique. This will make the JOURNAL more flexible so that it will lie open in the reader's hand.

All of these changes will result in no alteration in the number of characters set, even though there will be a slight reduction in the number of pages, from an average of 232 to 208. This new format will permit the Editors to accept neither more nor less material than formerly.

The Editors believe that the redesigning in these several respects will result in a greatly improved format for the JOURNAL. They wish to express their appreciation to the publishers for their careful study of this problem and for the results that are being achieved in making the JOURNAL a more easily read publication.

J. B.  
A. B.  
H. T.

## Reviews | Abstracts

*Edited by*

LOUIS M. HELLMAN, M.D.

### Books received for review

- Adaptation to Extrauterine Life** (Report of 31st Ross Conference on Pediatric Research). Edited by T. J. Oliver, Jr. 96 pages, 25 figures. Columbus, Ohio, 1959, Ross Laboratories.
- Anesthesia for Infants and Children.** By Robert M. Smith. 418 pages, 182 figures. St. Louis, 1959, The C. V. Mosby Company. \$12.00.
- Annales Universitatis Mariae Curie-Sklodowska, Volume 8.** By 40 contributing authors of Nakladem Uniwersytetu Marii Curie-Sklodowska. 469 pages. Lublin, Poland, 1959, Nakladem Uniwersytetu Marii Curie-Sklodowska.
- Avortements tardifs et accouchements prématurés.** By Otto Stamm. 130 pages, 37 figures, 14 tables. Paris, 1959, Masson et cie. 2.000 fr.
- Carcinogenesis—Mechanisms of Action.** By G. E. W. Wolstenholme and Maeve O'Connor, editors for the Ciba Foundation. 336 pages, 48 illustrations. Boston, 1959, Little, Brown & Company. \$9.50.
- Clinical Auscultation of the Heart.** By S. A. Levine and W. P. Harvey. Second edition. 657 pages, 660 figures. Philadelphia, 1959, W. B. Saunders Company. \$11.00.
- Clinical Obstetrics and Gynecology, Volume 2, Number 1, Spontaneous Abortion,** edited by David N. Danforth, and **Menstrual Disorders,** edited by C. Frederick Fluhmann. 256 pages, 50 figures, 9 tables. New York, 1959, Paul B. Hoeber, Inc. \$18.00 per year for 4 volumes.
- Clinical Obstetrics and Gynecology, Volume 2, Number 2, Genital Infections,** edited by George Schaefer, and **Prolonged Labor and Difficult Delivery,** edited by Clyde L. Randall. 596 pages, 49 figures, 13 tables. New York, 1959, Paul B. Hoeber, Inc. \$18.00 for set of 4 books per year.
- Combined Textbook of Obstetrics and Gynecology.** By Dugald Baird. Sixth edition. 936 pages, 492 illustrations. Baltimore, 1957, Williams & Wilkins Co. \$15.00.
- Diagnosis and Treatment of Menstrual Disorders and Sterility.** By Leon Israel. Fourth edition. 666 pages, 147 figures. New York, 1959, Paul B. Hoeber, Inc. \$15.00.
- Fundamentals of Gynecology.** By S. J. Behrman and J. R. G. Gosling. 416 pages, 166 figures. New York, 1959, Oxford University Press. \$9.50.
- Introductory Lectures in Medical Hypnosis.** By M. K. Bowers. 89 pages. New York, 1958, Institute for Research in Hypnosis. \$2.50.
- Mayes' Handbook for Midwives and Maternity Nurses.** Revised by F. D. Thomas. Sixth edition. 476 pages, 167 figures. Baltimore, 1959, Williams & Wilkins Co. \$5.50.
- Medical Management of the Menopause.** By Minnie B. Goldberg. 98 pages, 10 figures, 5 tables. New York, 1959, Grune & Stratton, Inc. \$4.50.
- Open Reduction of Common Fractures.** By Oscar P. Hampton, Jr., and William T. Fitts, Jr. 212 pages, 72 figures. New York, 1959, Grune & Stratton, Inc. \$8.75.
- Pediatric Pathology.** By Daniel Stowens. 676 pages, 374 figures. Baltimore, 1959, Williams & Wilkins Co. \$20.00.
- Physiology of the Newborn Infant.** By Clement A. Smith. Third edition. 497 pages, 62 figures, 60 tables. Springfield, 1959, Charles C Thomas, Publisher. \$12.50.
- Principles and Practice of Obstetric Anaesthesia.** By J. Selwyn Crawford. 128 pages, 2 figures, 2 tables. Springfield, 1959, Charles C Thomas, Publisher. \$4.00.
- Recent Progress in the Endocrinology of Re-**

- production.** Edited by C. W. Lloyd. 532 pages. New York, 1959, Academic Press, Inc. \$12.00.
- Regulation of Cell Metabolism.** By G. E. W. Wolstenholme and Cecilia M. O'Connor, editors for the Ciba Foundation. 387 pages, 109 illustrations. Boston, 1959, Little, Brown & Company. \$9.50.
- Relaxation and Exercise for Natural Childbirth.** By Helen Heardman. Second edition. 31 pages, 20 figures. Baltimore, 1959, Williams & Wilkins Co. 75 cents.
- Roentgens, Rads and Riddles—A Symposium on Supervoltage Radiation Therapy.** By M. Friedman, M. Brucer, and E. B. Anderson. 495 pages. Washington, D. C., 1959, Superintendent of Documents, U. S. Government Printing Office. \$3.50.
- 60 Jahre Medizinische Radiologie—Probleme und Empirie.** By Hans R. Schinz. 275 pages, 86 figures. Stuttgart, 1959, George Thieme Verlag. \$4.65.
- Die Sterilität der Frau—ein Leitfaden der Diagnostik und Therapie für die Praxis.** By W. Bickenbach and G. K. Doring, Eighth edition. Stuttgart, 1959, Georg Thieme Verlag. \$1.60.
- Strahlenbehandlung in der Gynäkologie.** By J. Ries and J. Breitner. 219 pages, 60 figures. München & Berling, 1959, Urban & Schwarzenberg. DM 32.
- The Surgeon and the Child.** By W. J. Potts. 225 pages, 22 illustrations. Philadelphia, 1959, W. B. Saunders Company. \$7.50.
- Symposium on Pulmonary Ventilation.** Edited by R. P. Harbord and R. Woolmer. 109 pages, 28 figures. Baltimore, 1959, Williams & Wilkins Co. \$4.00.
- A Synopsis of Anaesthesia.** By J. Alfred Lee. Fourth edition. 616 pages, 72 illustrations, Baltimore, 1959, Williams & Wilkins Co. \$6.50.
- A Synopsis of Obstetrics and Gynaecology.** By Aleck W. Bourne. Twelfth edition. 632 pages, 167 figures. Baltimore, 1959, Williams & Wilkins Co. \$8.00.
- Textbook of Pediatrics.** Edited by Waldo E. Nelson. Seventh edition. 1462 pages, 428 figures. Philadelphia, 1959, W. B. Saunders Company. \$16.50.
- 1958-1959 Series Year Book of Cancer.** By R. L. Clark, Jr., and R. W. Cumley. 570 pages, 202 figures. Chicago, 1959, Year Book Publishers, Inc. \$8.00.
- Your Care During Pregnancy.** By Norman F. Miller and Staff, Women's Hospital, University of Michigan Medical Center. 31 pages, 20 illustrations. Ann Arbor, 1959, Caduceus Press. 32 cents.

## Selected abstracts

### **Acta obstetrica et gynecologica scandinavica**

*Vol. 38, Fascia 1, 1959.*

\*Robbe, Hijordis: Physical Working Capacity, Blood Volume and Heart Volume in Cardiac Patients, p. 1.

Robbe: Physical Working Capacity, Blood Volume and Heart Volume in Cardiac Patients, p. 1.

Twenty-eight women with different types of heart disease were examined during pregnancy, labor, and the puerperium, and at about 8 months after delivery. Work-up of these patients included a wide variety of physiological tests. During pregnancy, the total blood volume and total amount of hemoglobin showed the

same mean increases as in normal pregnant women; 4 weeks after delivery stationary and normal values were found. The mean hemoglobin concentration was approximately normal during and after pregnancy. The increase of radiographic heart volume was slightly, but not significantly, greater in the cardiac patients than in normal women. After delivery the heart volume of the cardiac patients diminished more slowly than normally, and stationary values were not found until several months after delivery.

The physical working capacity in the groups of patients with septal defects, pulmonary stenosis, and aortic valvular disease remained approximately constant during and after pregnancy, except in 2 cases complicated by toxemia. In the group of mitral valvular disease, pure or combined with aortic valvular disease, there was

\*These articles have been abstracted.



a higher mean pulse rate response to any particular work load during pregnancy as compared with that in the nonpregnant state, thus implying a diminished physical working capacity during pregnancy in these patients.

In addition to the usual clinical examination of the pregnant cardiac patient, the author emphasizes that serial examinations utilizing the physiological tests outlined here are of considerable practical diagnostic and prognostic value.

Robert E. L. Nesbitt, Jr.

*Suppl. 2, 1959.*

\*Svennerud, Sven: Dysmenorrhea and Absenteeism, p. 7.

**Svennerud: Dysmenorrhea and Absenteeism, p. 7.**

The present study was made by questionnaire, personal interview, and gynecologic examination of 890 women aged 14 to 44 years. Most of the women were working in various branches of industry while the remainder belonged to the personnel of a theater or were pupils at a gymnastic institute.

Dysmenorrhea was noted in a total of 30.9 per cent. In 16.8 per cent it was nondisabling, in 8.3 per cent it was sometimes disabling, and in 5.8 per cent it was regularly disabling. It was most common (46.3 per cent) in the 20 to 24 year age class. In this group, dysmenorrhea was regularly disabling in 8.9 per cent. After age 25 the frequency decreased rapidly. In about 11 per cent of the total cases, dysmenorrhea was secondary to pelvic changes. The frequency of dysmenorrhea was about the same among women of widely different occupations. It often disappeared after pregnancy. Absenteeism because of dysmenorrhea represented only 1.1 days per year in factory workers and 0.3 day for office workers. Absence because of dysmenorrhea was highest in the lower age classes and among married women. Absence from this cause was found to be 3.7 per cent of the total absence for factory workers and 2.5 per cent for office workers. After 25 years of age absence because of dysmenorrhea decreased rapidly, and after 35 years of age it was less than 2 per cent of all absence. There was no difference found between the dysmenorrheic and nondysmenorrheic group regarding duration of employment in the same company, working capacity, and average wages. Also, the frequency of dysmenorrhea was not found to be influenced by environmental or emotional factors.

Robert E. L. Nesbitt, Jr.

## American Journal of Pathology

*Vol. 35, 1959.*

\*Cohen, Richard B., Chapman, William B., and Castleman, Benjamin: Hyperadrenocorticism (Cushing's Disease). A Study of Surgically Resected Adrenal Glands, p. 537.

**Cohen, Chapman, and Castleman: Hyperadrenocorticism (Cushing's Disease), p. 537.**

Hyperactive adrenal glands from 20 patients with Cushing's syndrome were examined. Control biopsy specimens were obtained from 14 patients during the course of retroperitoneal operations. Four pairs of adrenal glands from patients with Cushing's syndrome appeared normal grossly while all the rest exhibited evidence of hyperplasia.

The outstanding microscopic feature was a marked increase in the zona fasciculata at the expense of the zona glomerulus and sometimes extending into the medulla. Nodularity was seen frequently.

Although lipid distribution was similar to that of the normal control, there was some depletion of sudanophilic material, particularly cholesterol. Some of the glands contained atypical cells which were considered to indicate unusual stimulation.

It appears that nodular hyperplasia may in some cases precede the appearance of adenomas.

J. Edward Hall

## Anesthesiology

*Vol. 20, 1959.*

\*Bush, Robert C.: Caudal Analgesia for Vaginal Delivery. I. Organization, Medication, Technique, Maternal and Perinatal Mortality, p. 31.

\*Bush, Robert C.: Caudal Analgesia for Vaginal Delivery. II. Analysis of Complications, p. 186.

**Bush: Caudal Analgesia for Vaginal Delivery. I. Organization, Medication, Technique, Maternal and Perinatal Mortality, p. 31.**

The 24 hour coverage by private anesthesiologists in a 200 to 300 bed hospital with more than 15,000 of 28,000 deliveries managed with caudal analgesia is discussed. Supplementation with hypnotics and analgesics, techniques of administration of agents, criteria for beginning caudal analgesia, and management of complications are covered. The maternal death rate was 2.2 per 10,000 live births. Of the 6 maternal

deaths, one can be considered preventable (a cesarean section and hysterectomy for complete premature separation of the placenta; severe shock; dead baby; and operative hemorrhage), and this operation was performed under general anesthesia. The other maternal death that occurred with general anesthesia followed the rupture of an intracranial aneurysm. The uncorrected fetal perinatal loss was 27.5 per 1,000 births. Caudal anesthesia provided the infant whose birth weight was between 1 and 2 kilograms with the best chance of survival. For infants weighing over 2 kilograms at birth, the use of caudal analgesia was as safe as other methods of anesthetic management employed for vaginal delivery.

Harold Johnson

**Bush: Caudal Analgesia for Vaginal Delivery.**

**II. Analysis of Complications, p. 186.**

Of 11 years of 24 hour coverage by private anesthesiologists, the year 1956 was selected for analysis of complications because this year was representative of current practice of caudal analgesia and it afforded a reasonably large sample (12 per cent). Of 2,708 vaginal deliveries, 1,813 were with caudal analgesia. Maternal complications were subdivided into technical difficulties (inadvertent spinal, failures, or unsatisfactory analgesia), 8 per cent; hypotension, transient, 10 per cent; toxic reaction, nonserious; complications of labor, 3.7 per cent; postpartum complications (14 categories with number of cases were given). Perinatal complications were grossly divided into fetal distress characterized by changes in rate or rhythm of fetal heart sounds (2.6 per cent) and resuscitatory problems. Endotracheal intubation was done in 0.7 per cent (12 babies); 2 were stillborn; 2 died because of marked prematurity; one died from apparent birth injury; one died as a result of multiple congenital defects and atelectasis, and the last from unknown causes. Over-all, 3.2 per cent of babies delivered vaginally of mothers who received caudal analgesia during 1956 required resuscitation.

Harold Johnson

**Fertility and sterility**

*Vol. 10, March—April, 1959.*

\*Rutherford, R. N., Banks, A. L., and Coburn, W. A.: Primary Uterine Hypodevelopment Treated by Cyclic Hormone Therapy, p. 122.

\*Kurland, I. I., and Levine, W.: Hypothyroidism in Relation to Reproductive Disorders, p. 132.

\*Slater, S., Paz-Carranza, J., Solomons, E., and Perlmutter, M.: Effect of Hysterosalpingography on Assay of Thyroid Function, p. 144.

\*Hafez, E. S. E., Zarrow, M. X., and Pincus, G.: Experimental Attempts to Prolong Gestation in the Rabbit, p. 150.

\*Heiman, M.: Reproduction: Emotions and the Hypothalamic-Pituitary Function, p. 162.

**Rutherford, Banks, and Coburn: Primary Uterine Hypodevelopment Treated by Cyclic Hormone Therapy, p. 122.**

Six patients with measurable hypodevelopment of the uterus were treated with long-acting estrogens and progestogens for at least a year. The dose schedule was 20 mg. Delestrogen, followed by 250 mg. Delalutin 2 weeks later. Uterine measurements were taken every third month, at the onset of induced menstruation if possible. At those times specimens of endometrium were obtained for histologic study.

Success was achieved in 4 instances. This was arbitrarily set as the appearance of a 1:3 cervix-corpus relationship. In 3 successful cases the original cervix-corpus relationship was 1:2 and in the fourth patient 1:1.

Paul T. Topkins

**Kurland and Levine: Hypothyroidism in Relation to Reproductive Disorders, p. 132.**

Three hypothyroid patients with reproductive disorders were followed for 2, 10, and 12 years, respectively. One patient had adolescent hypothyroidism and the others postthyroidectomy hypothyroidism. Small doses of thyroid extract produced a stimulating effect on the pituitary-ovarian axis, whereas large doses had a depressing effect.

Paul T. Topkins

**Slater et al.: Effect of Hysterosalpingography on Assay of Thyroid Function, p. 144.**

A total of 28 clinically euthyroid patients was subjected to hysterosalpingography during the course of investigation of infertility, dysfunctional uterine bleeding, or some other gynecologic condition. Prior to instillation of the contrast medium, serum was obtained for a protein-bound iodine determination. Radioactive iodine

uptake values were also determined before hysterosalpingography was performed.

With an oil-soluble contrast medium, the radioactive iodine uptake values underwent a progressive decline or a marked depression as early as the second day after salpingography. The depression in the uptake of radioactive iodine lasted as long as 4 months and, in one patient, 7 months. Similarly, elevation of PBI was noticeable a day or two after salpingography and remained so for a long time. In one patient an elevated protein-bound iodine was still present 7 months after hysterosalpingography.

With water-soluble contrast media, there were marked elevations of PBI within 5 to 60 minutes after instillation of the dye, with reversion to normal limits within 24 to 48 hours. This coincided with complete absence of dye on the 24 hour films. No depression in the uptake of radioactive iodine was found during the study period, 2 to 20 days following salpingography.

*Paul T. Topkins*

**Hafez, Zarrow, and Pincus: Experimental Attempts to Prolong Gestation in the Rabbit, p. 150.**

The first experiment was concerned with an attempt to determine whether or not prolonged gestation could be induced in the rabbit by removal of about 50 per cent of the fetuses, leaving all the placentas and remaining fetuses intact.

Ten adult does were mated twice to fertile bucks and injected with an ovulating dose of sheep pituitary extract. Pregnancy was diagnosed 10 days post coitus by abdominal palpation. The animals were operated upon 5 to 15 days later, and all the fetuses removed from the left horn. The uterus was exposed and the fetus expelled through a small incision. The umbilical cord was crushed with a hemostat and the placentas left in situ. The animals were sacrificed on the thirty-sixth to the thirty-eighth day post coitus and the two uteri dissected. In 6 rabbits there was partial to complete resorption of the fetuses, owing perhaps to faulty operative technique. In 2 rabbits (20 per cent) one or more live fetuses were found, indicating the possibility of delaying parturition by removal of half the number of fetuses.

The second experiment was done to determine whether transplantation of blastocysts to the sterile horn of a pregnant rabbit following induced ovulation would result in implantation

and affect the gestation period.

Virgin does were superovulated by sheep pituitary extract, mated twice to fertile bucks and sacrificed 84 hours post coitus. The tubes and uterine horns were removed and flushed with a buffered Ringer's solution in order to obtain the fertilized ova. Sterility of the left uterine horn in the recipient does was insured by a salpingectomy of the left tube. The recipients were mated twice to fertile bucks as soon as practicable after the operation. On the twenty-fifth day post coitus the recipients were injected intravenously with 100 or 150 I. U. of human chorionic gonadotropin. From 10 to 15 healthy blastocysts were transplanted at the tubal end of the left uterus on the twenty-third, twenty-fifth, or twenty-seventh day post coitus. Most of the animals were sacrificed 38 days post coitus, and the uteri removed, flushed with saline, and then dissected. The wash fluid was examined carefully under the microscope for blastocysts. It was hoped that the new set of corpora lutea superimposed upon pregnancy would prepare suitable conditions for implantation in the left sterile horn. However, implantation failed to occur when the blastocysts were transplanted.

*Paul T. Topkins*

**Heiman: Reproduction: Emotions and the Hypothalamic-Pituitary Function, p. 162**

Recent investigation has provided evidence that the cells of the nuclei supraopticus and paraventricularis in the hypothalamus are the source of oxytocin. The hormone is then transported along the pituitary stalk toward the nerve terminals in the posterior pituitary. Here the hormone is stored and from here it is released. Oxytocin is capable of inducing an increase in uterine or tubal motility. This may occur at the thought of or during the act of intercourse. Animal experiments indicate that environmental stimuli, such as tactile stimuli of the mammary glands, vulva, and cervix, and conditioned stimuli are responsible for inducing secretion of the oxytocic hormone. In animals the hormone stimulates the motility of the estrogenized uterus, producing contraction waves from the cervix toward the Fallopian tubes, thereby facilitating sperm transport. Unfavorable emotional stimuli such as fright or excitement are known to impede lactation and milk ejection in lactating animals and humans. This is due to direct central inhibition of the release of oxytocin or to



its suppression by the intermediate action of adrenalin, which is released by emotional stress. The author suggests that blood assays of oxytocin (when the technique is sufficiently developed) obtained under varying conditions may provide a clue to the relationship between sexual activity and reproductive function.

*Paul T. Topkins*

### **German Medical Monthly**

*Vol. 4, 1959.*

\*Schwalm, H., and Schaudig, H.: Maternal Mortality in Germany, p. 47.

**Schwalm and Schaudig: Maternal Mortality in Germany, p. 47.**

Maternal mortality was the fourth greatest cause of death in women between ages 15 and 45 years with 1,184 deaths in West Germany in 1954. A table in the article shows that the only reporting country with a higher maternal mortality rate is Japan. In 1956 the rates were 16.8 and 13.9 per 10,000 live births respectively, for Japan and West Germany. The lowest rate recorded was 2.8 for the United States "white" population.

The authors have superficially investigated a part of the maternal death material of their country and found that: (1) 27 per cent of the deaths were due to toxemia; (2) 23 per cent of the deaths were due to hemorrhage; (3) 14.4 per cent of the deaths were due to puerperal infection; (4) 14.5 per cent of the deaths were due to "embolism"; (5) in 25 per cent of the fatalities a cesarean section had been performed; (6) maternal mortality was twice as great in small hospitals (100 or fewer deliveries per year) than in those hospitals having 500 or more deliveries per year; and (7) the number of women transferred by the midwife to the hospital varied from 4 per cent to 50 per cent.

*Schuyler G. Kohl*

### **Ginecologia y obstetricia de Mexico**

*Vol. 14, March-April, 1959.*

\*Reyes Ceja, Luis: A Trial of Labor in Patients With Previous Cesarean Section, p. 111.

**Reyes Ceja: A Trial of Labor in Patients With Previous Cesarean Section, p. 111.**

The author studied 190 unselected patients, the majority of whom were at term and who had had one or two previous cesarean sections. All of the patients were given a trial of labor and membranes were ruptured at 4 to 5 cm. dilatation. The duration of labor varied from 6 to

12 hours in women who had never had a vaginal delivery and from 3 to 6 hours in those patients who had had a previous vaginal delivery. Of the 190 patients, 118 were delivered spontaneously by the vaginal route. Forty-four were delivered by low forceps and 21 were delivered by elective midforceps. Only 4 of these patients showed prolonged labor and fetal distress and were delivered by repeat cesarean section. All of these 4 patients had had one previous cesarean section and had never had a vaginal delivery. Manual exploration of the uterus was carried out on all patients who had vaginal deliveries and no defects or ruptures were found. Four infants undergoing vaginal delivery presented by the breech. There were no maternal deaths. Five infants were dead on admission to the hospital. Three infants died neonatally and had marked fetal distress at the time of birth.

*Francis B. O'Brien*

### **Irish Journal of Medical Science**

*No. 402, June, 1959.*

\*Fleming, J. B.: Diverticulum of the Female Urethra, p. 286.

**Fleming: Diverticulum of the Female Urethra, p. 286.**

A diverticulum of the female urethra was at one time considered to be rare but since 1951 there has been an increased number of papers on the subject. Up to 1954 only one case had been described from Ireland. A questionnaire was sent to 59 gynecologists, 10 genitourinary surgeons, and 3 proctologists, and replies were received from all except 5, showing that 17 cases had been diagnosed and treated. In Ireland, to judge from the questionnaire, urethral diverticulum is an infrequent disorder.

In the further case now reported, the diagnosis had been missed on two previous occasions. The diverticulum was excised and bladder drainage was provided by a Foley catheter for 5 days. The patient had a normal convalescence, and at examination 7 months later no abnormality was noted and there had been no recurrence of symptoms.

*Edward Solomons*

### **Journal of the American Geriatrics Society**

*Vol. 7, March 1959.*

Cobb, Beatrix: Emotional Problems of Adult Cancer Patients, p. 274.



April, 1959.

\*Greenblatt, Robert B., and Scarpa-Smith, Clorinda, J.: Nymphomania in Postmenopausal Women, p. 339.

**Greenblatt and Scarpa-Smith: Nymphomania in Postmenopausal Women, p. 339.**

Two patients are reported, each of whom had an insatiable drive for sexual gratification although both were in the postmenopausal age group. The first, 65 years old, had hypertension but otherwise no abnormal physical or laboratory findings. The patient received 17-hydroxyprogesterone caproate intramuscularly twice weekly for 5 weeks and then 30 mg. of norethindrone daily. After a period she discontinued the drug and a period of bleeding lasting 6 days ensued. She then received 20 mg. norethindrone daily for several months. After 7 to 8 weeks of progestational therapy the sex drive lessened and has been held in abeyance since.

The second patient, aged 51, who had had her menopause 3 years previously, had an insatiable throbbing in the clitoris. The latter was not enlarged and appeared to be normal. Her physical and laboratory examinations were normal except that her blood pressure was 150/100. Because of the severity of her symptoms a clitoridectomy was done. After several injections of 17-hydroxyprogesterone caproate she took 30 mg. of norethindrone daily, reserpine, and premarin with meproamate. In this instance despite prolonged therapy the desire for sexual gratification has lessened only slightly.

The view is expressed that the androgens increase the libido in both males and females whereas progesterone or the corticoids, administered for a sufficiently long period of time, may bring about marked lessening of the sexual drive.

David M. Kydd

#### **Journal of Clinical Endocrinology and Metabolism**

Vol. 19, April 1959.

\*Moses, A. M., Lobotsky, J., and Lloyd, C. W.: Pre-eclampsia in a Bilaterally Adrenalectomized Woman, p. 987.

**Moses, Lobotsky, and Lloyd: Pre-eclampsia in a Bilaterally Adrenalectomized Woman, p. 987.**

A case is reported of pre-eclampsia developing during the eighth month of pregnancy in a woman who had undergone total bilateral adrenalectomy because of Cushing's syndrome.

During the time that she had pre-eclampsia, the levels of plasma and urinary 17-hydroxycorticosteroids were low. At the same time the urinary excretion of aldosterone, also low, was comparable to that reported for normal pregnancies in adrenalectomized women. Hypertension persisted in spite of withdrawal of adrenal steroid therapy and the development of adrenal insufficiency. These events cast doubt on the etiological role of the adrenal steroids in toxemia of pregnancy.

J. Edward Hall

#### **Journal of Pediatrics**

Vol. 54, March, 1959.

\*Gareau, F. E., Mackel, D. C., Boring, J. R., III, Payne, F. J., and Hammett, F. L.: The Acquisition of Fecal Flora by Infants from Their Mothers During Birth, p. 313.

**Gareau et al.: The Acquisition of Fecal Flora by Infants From Their Mothers During Birth, p. 313.**

Twenty mothers and their newborn infants delivered at the Grady Hospital in Atlanta were studied for bacteria fecal flora by hospital personnel and personnel from the Communicable Disease Center, U. S. Public Health Service.

Rectal swab specimens were obtained from the mother before delivery (both before and after enema when possible), but none after delivery. Throat and rectal swab specimens from the newborn infant were taken immediately after birth while the infant was still on the sterile field, and additional rectal swab specimens were taken at 24, 48, and 72 hours after birth.

Laboratory results showed that 25 per cent of the infants exhibited the same fecal flora as their mothers. The two mothers harboring pathogens in the intestinal tract apparently transferred them to their infants, for an enteropathogenic *Escherichia coli* was isolated from one infant in 48 hours and *Shigella* was cultured from another infant. In six instances there was correlation between the type specific organism in the fecal flora of the mother and newborn infant. In 13 instances there was a lack of such correlation.

Schuyler G. Kohl

April, 1959.

\*Geiger, Jacob: Erythroblastosis Fetalis Caused by Sensitization to Factor  $rh^W(C^W)$ , p. 484.

**Geiger: Erythroblastosis Fetalis Caused by Sensitization to Factor  $rh^W(C^W)$ , p. 484.**

A case of erythroblastosis fetalis caused by sensitization to the rare factor  $rh^W(C^W)$  in a seventh child is presented. This factor was present in the blood of the father and the third, fifth, and sixth child born to the mother, and to the seventh child discussed in this report. The significance of a positive direct antiglobulin test on cord blood and the value of routinely performing this test on blood of all newborn infants is emphasized.

*Schuyler G. Kohl*

*June, 1959.*

**\*Wallace, H. M., and Sanders, D.: Mortality Experience Among Children With Congenital Malformations, p. 801.**

**Wallace and Sanders: Mortality Experience Among Children With Congenital Malformations, p. 801.**

The authors present a study of 857 deaths attributed to congenital malformations reported in New York City in 1954. The causes of death were heart disease, 40 per cent; central nervous system conditions, 25 per cent; gastrointestinal conditions, 15 per cent; genitourinary system conditions, 5 per cent; cleft palate, 2 per cent; multiple malformations, 6 per cent; and miscellaneous, 7 per cent.

Fifty-two per cent of the deaths occurred within the neonatal period, 32 per cent in the postnatal period, 11 per cent in the preschool period, and 4 per cent in school age.

Correlations between hospital and death certificate diagnoses are presented, as are times of death for the various diagnoses. A preventability analysis showed 4.8 per cent to be "preventable" and another 8.2 per cent to be "probably preventable."

*Schuyler G. Kohl*

**Lancet**

*Vol. 1, April 4, 1959.*

**\*Ford, C. E., Jones, K. W., Miller, O. J., Mittwoch, U., Penrose, L. S., Ridler, M., and Shapiro, A.: The Chromosomes in a Patient Showing Both Mongolism and the Klinefelter Syndrome, p. 709.**

**\*Jacobs, P. A., Baikie, A. G., Court Brown, W. M., and Strong, J. A.: The Somatic Chromosomes in Mongolism, p. 710.**

**\*Ford, C. E., Jones, K. W., Polani, P. E., de Almeida, J. C., and Briggs, J. H.: A Sex-Chromosome Anomaly in a Case**

**of Gonadal Dysgenesis (Turner's Syndrome), p. 711.**

**Ford et al.: The Chromosomes in a Patient Showing Both Mongolism and the Klinefelter Syndrome, p. 709.**

Bone marrow specimens obtained from a patient who had the typical manifestations of both Klinefelter's syndrome and Mongolism were examined. Each cell contains 48 chromosomes (23 pairs as in a female with, in addition, a Y chromosome and an extra acrocentric chromosome). Thus, this patient who is now 45 years of age and in good health though an imbecile has two supernumerary chromosomes: an additional sex chromosome as found in Klinefelter's syndrome and a small chromosome which seems to be characteristic of Mongolism.

*David M. Kydd*

**Jacobs et al.: The Somatic Chromosomes in Mongolism, p. 710.**

The somatic chromosomes in 6 typical Mongols (3 males aged 41, 22, and 20 and 3 females aged 20, 20, and 16) were found to be 47 in number. The additional chromosome is acrocentric and in the smallest size range, and this extra chromosome appears to be characteristic of Mongolism.

*David M. Kydd*

**Ford et al.: A Sex-Chromosome Anomaly in a Case of Gonadal Dysgenesis (Turner's Syndrome), p. 711.**

The chromosomes were counted in 102 cells obtained from the bone marrow of a patient of 14 who had typical Turner's syndrome and were found to be 45 in number. In the 14 cells that were studied in detail there were 22 pairs and one odd chromosome. The authors suspected that the odd one was the X and that the sex-chromosome constitution of the patient was XO. As judged by the nuclear chromatin, the cells were "male" but the chromosomes were neither normally male nor normally female (no male component and but half a normal female component). Therefore chromatin negativity does not necessarily imply maleness. As an explanation for the development of this condition, nondisjunction such as has been described in *Drosophila melanogaster* is suggested. In the female fly nondisjunction implies the migration of two X chromosomes to one pole of the spindle. Thus, the ovum contains either the haploid number of autosomes plus two X chromosomes or only the

haploid number without X chromosomes. Fertilization of the latter by a Y-bearing sperm results in a nonviable YO zygote and by an X-bearing sperm results in an XO zygote which becomes a sterile male. The suggestion is made that in man the XO zygote develops into a sterile "gonadal" individual whose phenotype is female. Fertilization of the other abnormal ovum (XX) by X-bearing sperm would yield XXX which has not been found so far in man, but XXY has been described in Klinefelter's syndrome.

David M. Kydd

**Proceedings of the Society for  
Experimental Biology and Medicine**

Vol. 100, January, 1959.

\*Graham, T. M., Marks, A., and Ershoff, B. H.: Effects of Prenatal X-Irradiation on Discrimination Learning in the Rat, p. 78.

Graham, Marks, and Ershoff: Effects of Prenatal X-Irradiation on Discrimination Learning in the Rat, p. 78.

The offspring of rats irradiated during pregnancy were subjected to a brightness discrimination problem at 6 months of age. They were compared to nonirradiated controls.

The nonirradiated rats achieved the criterion (80 per cent correct responses in discriminating a bright from a dim light for 2 consecutive days) on Day 9. The rats irradiated with 150 r x-irradiation on the tenth or the eighteenth day of pregnancy achieved the criterion on Day 10. Those irradiated on Day 14 with 150 r and on Day 18 with 300 r did not achieve the criterion by Day 12. Furthermore, the latter two groups could not accomplish the criterion of an absolute discrimination problem (i.e., the presence or absence of light) in an additional 4 days.

It is demonstrated that rats which are irradiated prenatally will show a lessened capacity for learning a brightness discrimination problem.

Louis A. Gentile

March, 1959.

\*Assali, N. S., and Ross, M.: Nitrous Oxide Solubility in Fetal and Uterine Tissues in Human Pregnancy, p. 497.

\*Shetlar, M. R., Lacefield, E. G., White, B. N., and Schilling, J. A.: Wound Heal-

ing: Glycoproteins of Wound Tissue. I. Studies of Hexosamine, Hexose, and Uronic Acids Content, p. 501.

Assali and Ross: Nitrous Oxide Solubility in Fetal and Uterine Tissues in Human Pregnancy, p. 497.

The authors adopted Kety's formula, which was originally used to calculate cerebral blood flow, to measure uterine blood flow in human pregnancy.

The Bunsen coefficient was calculated for various fetal tissues and the placenta, cord, and myometrium in one immature, one premature, and one full-term fetus. The authors demonstrated that the 10<sub>2</sub>0 solubility coefficient varies considerably from one tissue to another but is the same no matter the age of the fetus. The mean for all tissues was 0.430 and the study gave a N<sub>2</sub>O partition coefficient between whole pregnant uterus and blood of 1.043.

Louis A. Gentile

Shetlar et al.: Wound Healing: Glycoproteins of Wound Tissue. I. Studies of Hexosamine, Hexose, and Uronic Acids Content, p. 501.

This study demonstrates the hexosamine, hexose, and uronic acid content in wound tissue formed around stainless steel cylinders at different stages of wound repair. It was found that uronic acid (expressed as glucuronic acid) is relatively low at 7 days, is maximum at 28 days, and remains constant for at least 42 days. Hexosamine and hexose levels are high at 7 days and do not strikingly increase thereafter. Paper electrophoresis of monosaccharides of hydrolysates of wound tissue revealed weak bands of uronic acid as compared to strong bands of glucose, mannose, and galactose. The uronic acid band was stronger in the later samples.

Louis A. Gentile

**Surgery, Gynecology and Obstetrics**

Vol. 108, January, 1959.

Ginsberg, Victor, and Harmel, Merel H.: A Six Year Study of Incompatible Blood Transfusions, p. 19.

March, 1959.

Schmitz, H. E., Schmitz, R. L., Smith, C. J., and Molitor, J. J.: The Technique of Synchronous (Two Team) Abdominoperineal Pelvic Exenteration, p. 351.

## Items

### **American Board of Obstetrics and Gynecology**

The next scheduled examinations (Part II), oral and clinical, for all candidates, will be conducted at the Edgewater Beach Hotel, Chicago, Illinois, by the entire Board from April 11 through 16, 1960. Formal notice of the exact time of each candidate's examination will be sent him in advance of the examination dates.

Candidates who participated in the Part I examinations will be notified of their eligibility for the Part II examinations as soon as possible.

Current Bulletins of the American Board of Obstetrics and Gynecology, outlining the requirements for application, may be obtained by writing to the Secretary.

*Robert L. Faulkner, M.D., Secretary  
2105 Adelbert Road  
Cleveland 6, Ohio*

### **New clinical center study on the Stein-Leventhal syndrome**

An investigation of the role of the adrenal gland in the Stein-Leventhal syndrome has been initiated at the Clinical Center, National Institutes of Health. Physicians interested in referring laparotomy-proved cases should write or

telephone: J. E. Rall, M.D., or Saul W. Rosen, M.D., National Institute of Arthritis and Metabolic Diseases, Bethesda 14, Maryland.

### **Pan American conference on infertility**

The Pan American Conference on Infertility, sponsored by the International Fertility Association, will be held Jan. 10-14, 1960, at Eden Roc Hotel, Miami Beach, Florida. For information, write Maxwell Roland, M.D., Chairman of Registration, 109-23 71st Road, Forest Hills 75, New York.

### **Teaching slides on the exfoliative cytology of the female genital tract**

One hundred teaching slides, "The Exfoliative Cytology of the Female Genital Tract," can be obtained on loan from each of the Divisions of the American Cancer Society.

These slides were developed for teaching purposes by Leopold G. Koss, M.D., and Grace R. Durfee, B.S., of the Memorial Center for Cancer and Allied Diseases in New York City.

Inquiries for the loan of this set should be addressed to the local Division of the American Cancer Society.



# Roster of American obstetrical and gynecological societies\*

(Appears in January and July)

**American College of Obstetricians and Gynecologists.** (1951) *President*, R. Glenn Craig. *Secretary*, John C. Ullery, Starling-Loving Bldg., The Ohio State University, Columbus, Ohio.

**American Gynecological Society.** (1876) *President*, Karl H. Martzloff. *Secretary*, Andrew A. Marchetti, Georgetown University Hospital, Washington 7, D. C. Annual meeting, May 30, 31, and June 1, 1960, Williamsburg, Va.

**American Association of Obstetricians and Gynecologists.** (1888) *President*, Robert A. Ross, Chapel Hill, N. C. *Secretary*, Clyde L. Randall, 216 Summer St., Buffalo 22, N. Y.

**Central Association of Obstetricians and Gynecologists.** (1929) *President*, Isadore Dyer, New Orleans, La. *Secretary*, Herman L. Gardner, 633 Hermann Professional Bldg., Houston 25, Texas. Annual meeting, Hotel Muehlebach, Kansas City, Mo., Oct. 6-8, 1960.

**South Atlantic Association of Obstetricians and**

**Gynecologists.** (1938) *President*, C. H. Mauzy. *Secretary*, W. Norman Thornton, Jr., University of Virginia Hospital, Charlottesville, Va. Next meeting Jan. 31-Feb. 3, 1960, Hollywood Beach Hotel, Hollywood, Fla.

**A. M. A. Section on Obstetrics and Gynecology.** (1859) *Chairman*, Curtis J. Lund, Rochester, N. Y. *Secretary*, Keith P. Russell, 511 S. Bonnie Brae St., Los Angeles 57, Calif. Next meeting, June 13-17, 1960, Miami Beach, Fla.

**Society of Obstetricians and Gynaecologists of Canada.** (1944) *President*, D. E. Cannell. *Secretary*, F. P. McInnis, 280 Bloor St., W., Toronto 5, Ont. Annual meeting, Jasper Park Lodge, June 9-12, 1960.

**American Board of Obstetrics and Gynecology, Inc.** (1930) *President*, F. Bayard Carter. *Secretary*, Robert L. Faulkner, 2105 Adelbert Rd., Cleveland 6, Ohio. Next meeting April 11-16, 1960.

**Akron Obstetrical and Gynecological Society.** (1946) *President*, Carl J. Paternite. *Secretary*, Edson A. Freeman, 2032 Chestnut Blvd., Cuyahoga Falls, Ohio. Meetings, third Friday, January, April, June, and October.

**Alabama Association of Obstetricians and Gynecologists.** (1940) *President*, Julian P. Hardy. *Secretary*, Lyman Findley, 819 Fourth Ave., Tuscaloosa, Ala.

**Alameda County Gynecological Society.** (1951) *President*, Samuel P. Hall. *Secretary*, Samuel C. Iwig, 1300 Bancroft Ave., San Leandro, Calif. Meetings, fourth Wednesday, September

through May.

**Arkansas Obstetrical and Gynecological Society.** (1953) *President*, J. B. Kittrell. *Secretary*, Ruth Lesh, 221 N. College, Fayetteville, Ark. Meetings, spring and fall.

**Atlanta Obstetrical and Gynecological Society.** (1954) *President*, Emmett Durham Colvin. *Secretary*, Stephen T. Barnett, Jr., 478 Peachtree St., N.E., Atlanta, Ga. Meetings, October, February, April, and June.

**Birmingham Obstetrical and Gynecological Society.** (1949) *President*, Walter Batson. *Secretary*, John Hodo, 825 28th Ave., S., Homewood, Ala. Meetings, February and April.

**Boston, Obstetrical Society of.** (1861) *President*, Langdon Parsons. *Secretary*, A. Gordon Gauld, 1180 Beacon St., Brookline 46, Mass. Meetings, third Monday, January, February, March, April, October, and November.

\*Changes, omissions, and corrections must be received by the publisher two months in advance, by May 1 for the July Roster and by November 1 for the January Roster. Please address The C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, Missouri. The number after the Society's name is the year of founding. For further information, address the respective secretaries.

**Bronx Gynecological and Obstetrical Society.** (1924) *President*, A. Charles Posner. *Secretary*, William J. Farrell, 2980 Valentine Ave., Bronx 58, N. Y. Meetings, fourth Monday, January, February, March, April, October, and November.

**Brooklyn Gynecological Society, Inc.** (1890) *President*, Louis M. Hellman. *Secretary*, Warren A. Lapp, 731 E. 22nd St., Brooklyn 10, N. Y. Meetings, third Wednesday, January, February, March, April, May, October, and November.

**Buffalo Obstetrical and Gynecological Society.** (1946) *President*, Louis G. Farris. *Secretary*, Richard W. Baetz, 216 Summer St., Buffalo 22, N. Y. Meetings, first Tuesday, September through May.

**Central New York Association of Gynecologists and Obstetricians.** (1938) *President*, Vincent J. Hemmer. *Secretary*, James N. Capps, 325 University Ave., Syracuse 10, N. Y. Meetings, first Tuesday, September, November, January, March, and May.

**Chicago Gynecological Society.** (1878) *President*, Clyde J. Geiger. *Secretary*, William G. Cummings, 636 Church St., Evanston, Ill. Meetings, third Friday, October through June.

**Cincinnati Obstetrical and Gynecological Society.** (1876) *President*, Edward Alberts. *Secretary*, Douglas P. Graf, 1035 Carew Tower, Cincinnati 2, Ohio. Meetings, third Thursday, September through June.

**Cleveland Society of Obstetrics and Gynecology.** (1947) *President*, Eduard Eichner. *Secretary*, Richard Glove, 3550 Warrensville Center Rd., Shaker Heights 22, Ohio. Meetings, fourth Monday, September, November, January, March, and May.

**Columbus Obstetrical and Gynecological Society.** (1944) *President*, Harry E. Ezell. *Secretary*, Wm. E. Copeland, University Hospital, Columbus, Ohio. Meetings, fourth Wednesday of month, September through June.

**Connecticut Society of American Board Obstetricians and Gynecologists, Inc.** (1952) *President*, Louis F. Middlebrook, Jr. *Secretary*, Joseph Klein, 435 Farmington Ave., Hartford 5, Conn. Meetings, April and November.

**Dallas-Fort Worth Gynecologic and Obstetric Society.** (1948) *President*, T. D. Mato. *Secretary*, James T. Downs, III, 3707 Gaston Ave., Dallas 10, Texas. Meetings, spring and fall.

**Dayton Obstetrical and Gynecological Society.** (1937) *President*, William V. Lingle. *Secre-*

*tary*, Arthur Sartorius, 117 S. Main St., Dayton, Ohio. Meetings, third Wednesday each month, Van Cleve Hotel.

**Denver Gynecological and Obstetrical Society.** (1942) *President*, Freeman H. Longwell. *Secretary*, George M. Horner, 3705 E. Colfax Ave., Denver, Colo. Meetings, first Monday of every month.

**Florida Obstetric and Gynecologic Society.** (1948) *President*, Homer L. Pearson, Jr. *Secretary*, Sam W. Denham, 1661 Riverside Ave., Jacksonville 4, Fla. Meetings, April 9 and 10, December, 1960.

**Georgia State Obstetrical and Gynecological Society.** (1951) *President*, E. Carson Demmond. *Secretary*, C. I. Bryans, Jr., 1139 Druid Park Ave., Augusta, Ga. Meetings, spring and fall.

**Harris, John Warton, Obstetrical Society.** (1953) *President*, William V. Luetke. *Joint Secretaries*, Madeline Thornton and William Keikhofer, State of Wisconsin General Hospital, 1300 University Ave., Madison, Wis. Annual meeting in May.

**Honolulu Obstetrical and Gynecological Society.** (1947) *President*, Richard Sakimoto. *Secretary*, John Ohtani, Rm. 410, Professional Center Bldg., 1481 S. King St., Honolulu 14, Hawaii. Meetings, third Monday of each month, Mabel Smythe Bldg.

**Houston Gynecological and Obstetrical Society.** (1956) *President*, Arthur M. Faris. *Secretary*, William R. Knight, III, 724 Hermann Professional Bldg., Houston 25, Texas. Meetings by announcement.

**Indiana Obstetrical and Gynecological Society.** (1947) *President*, Paul F. Muller. *Secretary*, Floyd T. Romberger, Jr., 3440 N. Meridian St., Indianapolis 8, Ind. Meetings, January and May.

**Interurban Obstetrical and Gynecological Society.** (1949) *President*, Herbert Burwig, Buffalo, N. Y. *Secretary*, E. R. Duggan, 16 N. Goodman St., Rochester 7, N. Y. Meeting, October, 1960.

**Iowa Obstetrical and Gynecological Society.** (1947) *President*, Walter J. Balzer. *Secretary*, Clifford P. Goplerud, University Hospitals, Iowa City, Iowa.

**Kansas City Gynecological Society.** (1922) *President*, H. Kermit Knoch. *Secretary*, Robert C. Buckner, 4620 J. C. Nichols Parkway, Kansas City 12, Mo. Meetings, Jan. 21, March 24, and May 5, 1960.

**Kentucky Obstetrical and Gynecological Society.**

- (1947) *President*, Joseph Liebman, Frankfort, Ky. *Secretary*, Ed. Masters, 107 Fairmeade Rd., Louisville, Ky. Annual meeting in April.
- Long Beach Obstetrical and Gynecological Society.** (1954) *President*, Donald Crawford. *Secretary*, Daniel M. O'Toole, 2240 Pacific Ave., Long Beach, Calif. Meetings, fourth Tuesday every second month.
- Los Angeles Obstetrical and Gynecological Society.** (1914) *President*, Dan Golenternek. *Secretary*, Leon J. Shulman, 5478 Wilshire Blvd., Room 222, Los Angeles 36, Calif. Meetings, second Tuesday, September, November, January, March, and May.
- Louisville Obstetrical and Gynecological Society.** (1923) *President*, W. P. Eubank. *Secretary*, Edward Bell, Medical Arts Bldg., Louisville, Ky. Meetings, fourth Monday, October, November, January, February, March, April, and May.
- Madison Obstetrical and Gynecological Society.** (1950) *President and Secretary*, John Healy, Madison, Wis. Meetings, second Tuesday each month.
- Maryland Obstetrical and Gynecological Society.** (1929) *President*, William Stephens. *Secretary*, D. Frank Kaltreider, University Hospital, Lockwood and Greene Sts., Baltimore, Md. Meetings, September, November, January, March, and May.
- Memphis Obstetrical and Gynecological Society.** (1950) *President*, Walter A. Ruch. *Secretary*, Robert M. Ruch, 509B Baptist Medical Bldg., 20 S. Dudley, Memphis, Tenn. Meetings, second Tuesday, October through May.
- Miami Obstetrical and Gynecological Society.** (1946) *President*, Henry H. Caffee. *Secretary*, Norman McLeod, 249 Sevilla Ave., Coral Gables, Fla. Meetings, second Thursday, January, March, May, and November.
- Michigan Society of Obstetricians and Gynecologists.** (1924) *President*, C. Paul Hodgkinson. *Secretary*, Robert G. Swanson, 936 Alter Rd., Detroit 15, Mich. Meetings, Feb. 2, April 5, and May 3, 1960.
- Milwaukee Gynecological Society.** (1951) *President*, Benjamin E. Urdan. *Secretary*, John Thoma, 411 E. Mason St., Milwaukee 2, Wis. Meetings, last Monday, November, January, March, and April.
- Minneapolis Obstetrical and Gynecological Society.** (1955) *President*, Maxwell Barr. *Secretary*, Richard R. Flihr, 301 Doctors Bldg., Minneapolis 2, Minn. Meetings, November, January, March, and May.
- Minnesota Obstetrical and Gynecological Society.** (1936) *President*, Eduard A. Banner. *Secretary*, Alex Barno, 4959 Excelsior Blvd., Minneapolis 16, Minn. Meetings, April and November.
- Mississippi Obstetrical and Gynecological Society.** (1947) *President*, Carl Lewis. *Secretary*, Blanche Lockard, 838 Lakeland Drive, Jackson, Miss. Meetings, May and November.
- Mobile County Obstetrical and Gynecological Society.** (1949) *President*, O. M. Otts, Jr. *Secretary*, A. K. Conditt, 1367 Government St., Mobile, Ala. Meetings, quarterly when called.
- Montgomery County (Ohio) Obstetrical and Gynecological Society.** (1937) *President*, L. O. Fredericks. *Secretary*, A. A. Kunnen, 406 Harries Bldg., Dayton, Ohio. Meetings, third Wednesday of each month.
- Montana State Obstetrical and Gynecological Society.** (1946) *President*, Richard L. Peterson. *Secretary*, Joseph H. Brancamp, Mayer Bldg., 10 S. Idaho, Butte, Mont. Next meeting, May, 1960.
- Nashville Obstetrical and Gynecological Society.** (1955) *President*, Edwin L. Williams. *Secretary*, B. K. Hibbett, 2122 W. End Ave., Nashville 5, Tenn. Meetings, first Tuesday in March, June, October, and December.
- Nassau Obstetrical Society.** (1944) *President*, A. Franklin Rowsom. *Secretary*, Joseph A. Mellow, 1554 Northern Blvd., Manhasset, N. Y. Meetings, Feb. 18 and April 18, 1960.
- New England Obstetrical and Gynecological Society.** (1929) *President*, Clyde Swett, Island Falls, Maine. *Secretary*, William A. Lynch, 1101 Beacon St., Brookline 46, Mass. Meetings, spring and fall.
- New Haven Obstetrical Society.** (1946) *President*, Michael H. Lavorgna. *Secretary*, David J. Kreis, 59 Trumbull St., New Haven, Conn. Meetings, third Tuesday, September, November, January, March, and May.
- New Jersey Obstetrical and Gynecological Society.** (1947) *President*, Henry S. Acken, Jr. *Secretary*, Saul B. Gusberg, 180 Fort Washington Ave., New York 32, N. Y. Meetings, second Tuesday, October through May.
- New Mexico Obstetrical and Gynecological Society.** (1947) *President*, Howard L. Smith. *Secretary*, Henry R. Hyslop, 313 W. Country Club Rd., Roswell, N. Mex. Meetings, quarterly.
- New Orleans Gynecological and Obstetrical So-**



ciety. (1924) *President*, Jason Collins. *Secretary*, Julius T. Davis, Jr., 4414 Magnolia St., New Orleans 15, La. Meetings, October, November, January, March, and May.

**New York Obstetrical Society.** (1863) *President*, Carl T. Javert. *Secretary*, S. B. Gusberg, 180 Fort Washington Ave., New York, N. Y. Meetings, second Tuesday, October through May.

**North Carolina Obstetrical and Gynecological Society.** (1932) *President*, Walter L. Thomas. *Secretary*, Kenneth A. Podger, Durham, N. C. Next meeting, Mid Pines Club, Southern Pines, N. C., April 29–May 1, 1960.

**North Dakota Society of Obstetrics and Gynecology.** (1938) *President*, James H. Mahoney. *Secretary*, G. Wilson Hunter, Fargo Clinic, Fargo, N. D. Meetings, May 2, 3; Sept. 9, 10, 1960.

**Northeastern New York Obstetrical and Gynecological Society.** (1935) *President*, James H. Flynn. *Secretary*, D. F. O'Keeffe, 153 Bay St., Glens Falls, N. Y. Meetings, fourth Thursday, January, April, and September.

**Northern California Obstetrical and Gynecological Society.** (1955) *President*, Warren E. Jones. *Secretary*, Andrew M. Henderson, Jr., 2901 Capitol Ave., Sacramento, Calif. Meetings, January, April, July, and October.

**Oklahoma City Obstetrical and Gynecological Society.** (1940) *President*, Milton Serwer. *Secretary*, Charles D. Bodine, 1220 N. Walker, Oklahoma City, Okla. Meetings, third Monday each month.

**Omaha Obstetrical and Gynecological Society.** (1947) *President*, Walter J. Holden. *Secretary*, William Boelter, 525 Doctors Bldg., Omaha, Neb. Meetings, third Wednesday, January, March, May, September, and November.

**Oregon Society of Obstetricians and Gynecologists.** (1946) *President*, John Kirk. *Secretary*, Richard Franklin, 1735 N. Wheeler Ave., Portland, Ore. Meetings, third Friday, October through May, except December.

**Pacific Coast Obstetrical and Gynecological Society.** (1931) *President*, George Judd, Los Angeles. *Secretary*, Keith Russell, 511 S. Bonnie Brae St., Los Angeles 57, Calif. Meeting, Sept. 27–30, 1960.

**Pacific Northwest Obstetrical and Gynecological Association.** (1947) *President*, Earl Hall. *Secretary*, Clifford L. Fearl, 1133 S.W. Market St., Portland 1, Ore. Next meeting, Vancouver, B. C., June, 1960.

**Philadelphia, Obstetrical Society of.** (1868)

*President*, Paul O. Klingensmith. *Secretary*, John P. Emich, Jr., 155 W. Walnut Lane, Philadelphia 44, Pa. Meetings, first Thursday, of each month.

**Pittsburgh Obstetrical and Gynecological Society.** (1934) *President*, Michael A. Guthrie. *Secretary*, Travis A. French, 405-B First Federal Plaza, New Castle, Pa. Meetings, first Monday, October through May.

**Portland Society of Obstetricians and Gynecologists.** (1928) *President*, David W. James. *Secretary*, Ivan W. Langley, 728 Medical Arts Bldg., Portland 5, Ore. Meetings, fourth Wednesday, September through May.

**Queens Gynecological Society.** (1948) *President*, David A. Conners. *Secretary*, B. Edmond Thomas, 30 Grace Ave., Great Neck, N. Y. Meetings, second Wednesday, October, December, February, and April.

**Rochester Obstetrical and Gynecological Society.** (1939) *President*, John Hamilton. *Secretary*, William Lange, 16 N. Goodman St., Rochester 7, N. Y. Meetings, monthly on Tuesday.

**St. Louis Gynecological Society.** (1924) *President*, George J. L. Wulff, Jr. *Secretary*, Bryce H. Bondurant, 950 Francis Pl., Clayton, Mo. Meetings, Feb. 11 and April 14, 1960, Congress Hotel.

**San Antonio Obstetrical and Gynecological Society.** *President*, G. G. Passmore. *Secretary*, Frank M. Posey, Jr., 101 N. McCollough, San Antonio, Texas.

**San Diego Gynecological Society.** (1937) *President*, George R. Turner. *Secretary*, Francis L. Rook, 3650 Clairmont Dr., San Diego 17, Calif. Meetings, third Friday of month.

**San Francisco Gynecological Society.** (1929) *President*, Charles McLennan. *Secretary*, Carl Goetsch, 2915 Telegraph Ave., Berkeley 5, Calif. Meetings, second Friday, October through May.

**Seattle Gynecological Society.** (1941) *President*, R. N. Rutherford. *Secretary*, Walter Keifer, 1115 Boylston, Seattle, Wash. Meetings, third Wednesday each month.

**South Carolina Obstetrical and Gynecological Society.** (1946) *President*, David F. Watson. *Secretary*, Albert J. Baroody, 352 W. Palmetto St., Florence, S. C. Next meeting, October, 1960.

**South Dakota Society of Obstetrics and Gynecology.** (1952) *President*, H. Benjamin Munson. *Secretary*, H. H. Theissen, 728 Columbus



- St., Rapid City, S. D. Meetings, May and September.
- Southeastern Obstetrical and Gynecological Society.** *President*, John R. McCain. *Secretary*, T. Bert Fletcher, Jr., 1203 Miccosukee Rd., Tallahassee, Fla. Meeting, April, 1960.
- Southern California, Obstetrical and Gynecological Assembly of.** (1945) *President*, A. M. McCausland. *Secretary*, Keith P. Russell, 511 S. Bonnie Brae St., Los Angeles 57, Calif. Next meeting, Los Angeles, Feb. 8-12, 1960.
- Southwest Obstetrical and Gynecological Society.** (1951) *President*, Charles Newcomb. *Secretary*, Zeph. B. Campbell, 550 W. Thomas Rd., Phoenix, Ariz. Next meeting, Las Vegas, Nev., Nov. 6-8, 1960.
- Tennessee State Obstetrical and Gynecological Society.** *President*, Homer Pace. *Secretary*, J. W. Ellis, 2122 W. End Ave., Nashville 5, Tenn. Meetings, yearly in April.
- Texas Association of Obstetricians and Gynecologists.** (1930) *President*, Maurice I. Meynier, Jr., Houston, Texas. *Secretary*, Hugh W. Savage, 815 Fifth Ave., Ft. Worth, Texas. Annual meeting, Austin, Texas, Feb. 13 and 14, 1960.
- Tulsa Obstetrical and Gynecological Society.** (1955) *President*, Houston F. Mount. *Secretary*, Robert E. Dillman, 21st St. Doctors Bldg., Tulsa, Okla. Meetings, second Wednesday, January, March, and May.
- Utah Obstetrical and Gynecological Society.** (1948) *President*, W. J. Jones. *Secretary*, E. Conrad Monson, 2955 Harrison Blvd., Ogden, Utah. Meetings, September, December, February, and May.
- Virginia Obstetrical and Gynecological Society.** (1936) *President*, William D. Suggs. *Secretary*, Brock D. Jones, Jr., 1204 Colonial Ave., Norfolk 17, Va. Meetings, April and October.
- Washington Gynecological Society.** (1933) *President*, John L. Parks. *Secretary*, Robert B. Nelson, Jr., 1824 Massachusetts Ave., N.W., Washington 6, D. C. Meetings, January, March, and May.
- Washington State Obstetrical Association.** (1936) *President*, Charles Ward Day. *Secretary*, Donald M. McIntyre, 1120 Cherry St., Seattle 4, Wash. Meetings, April and October, 1960.
- West Texas Obstetrical and Gynecological Society.** (1954) *President*, R. Lee Rode. *Secretary*, Wm. C. Smith, 3801 Nineteenth St., Suite 119, Lubbock, Texas. Meeting, November, 1960.
- Westchester Obstetrical and Gynecological Society.** (1939) *President*, Edwin A. Haverty. *Secretary*, Norman M. Weinrod, 175 Crary Ave., Mt. Vernon, N. Y. Meetings, Feb. 10, March 9, and May 11, 1960.
- Wisconsin Society of Obstetrics and Gynecology.** (1940) *President*, Ralph E. Campbell, Madison, Wis. *Secretary*, William C. Mussey, 113 N. Carroll Ave., Madison 3, Wis. Spring meeting in conjunction with the Wisconsin State Medical Society.



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1. Kistner, R. W.: Conservative Treatment of Endometriosis, *Postgrad. Med.* 24:505 (Nov.) 1958.
2. Southam, A. L.: Symposium on Enovid: Clinical Application of Enovid and Other Progestational Agents in Control of Menstrual Disorders, Chicago, Searle Research Laboratories, 1959, pp. 11-14.
3. Roland, M.: Effects of Norethynodrel on the Human Endometrium, *Ann. New York Acad. Sc.* 71:638 (July 30) 1958.
4. Kupperman, H. S., and Epstein, J. A.: A Symposium on 19-Nor Progestational Steroids: Gonadotropic-Inhibiting and Uterotropic Effects of Enovid, Chicago, Searle Research Laboratories, 1957, pp. 32-45.
5. Weinberg, C. H.: Symposium on Enovid: Enovid for Relief of Dysmenorrhea and Control of Dysfunctional Bleeding and Endometriosis, Chicago, Searle Research Laboratories, 1959, pp. 19-24.
6. Greenblatt, R. B.: Symposium on Enovid: Progesterone and Progestins: Their Limitations and Comparative Values, Chicago, Searle Research Laboratories, 1959, pp. 4-10.



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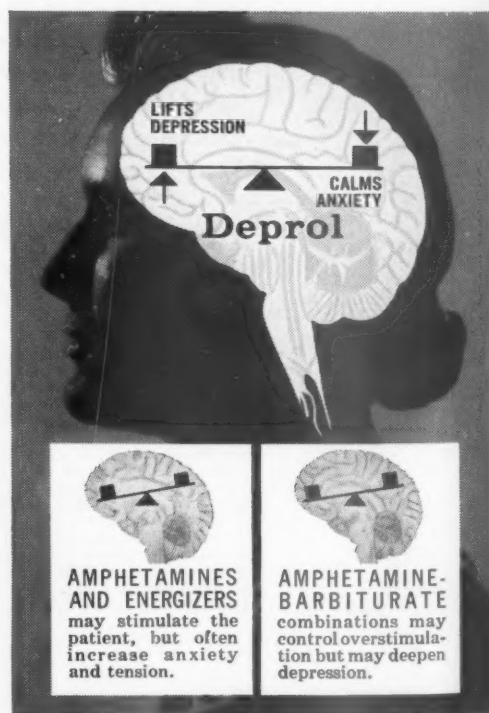
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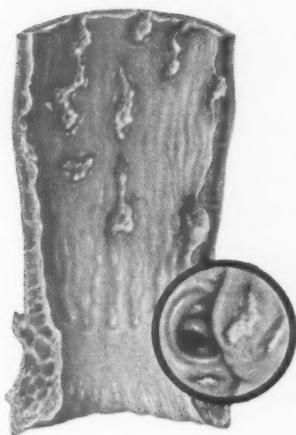
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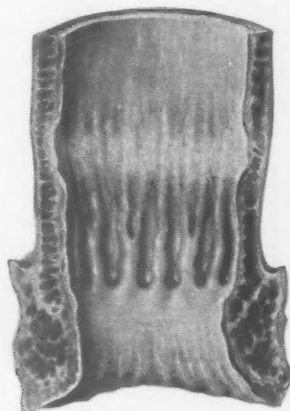
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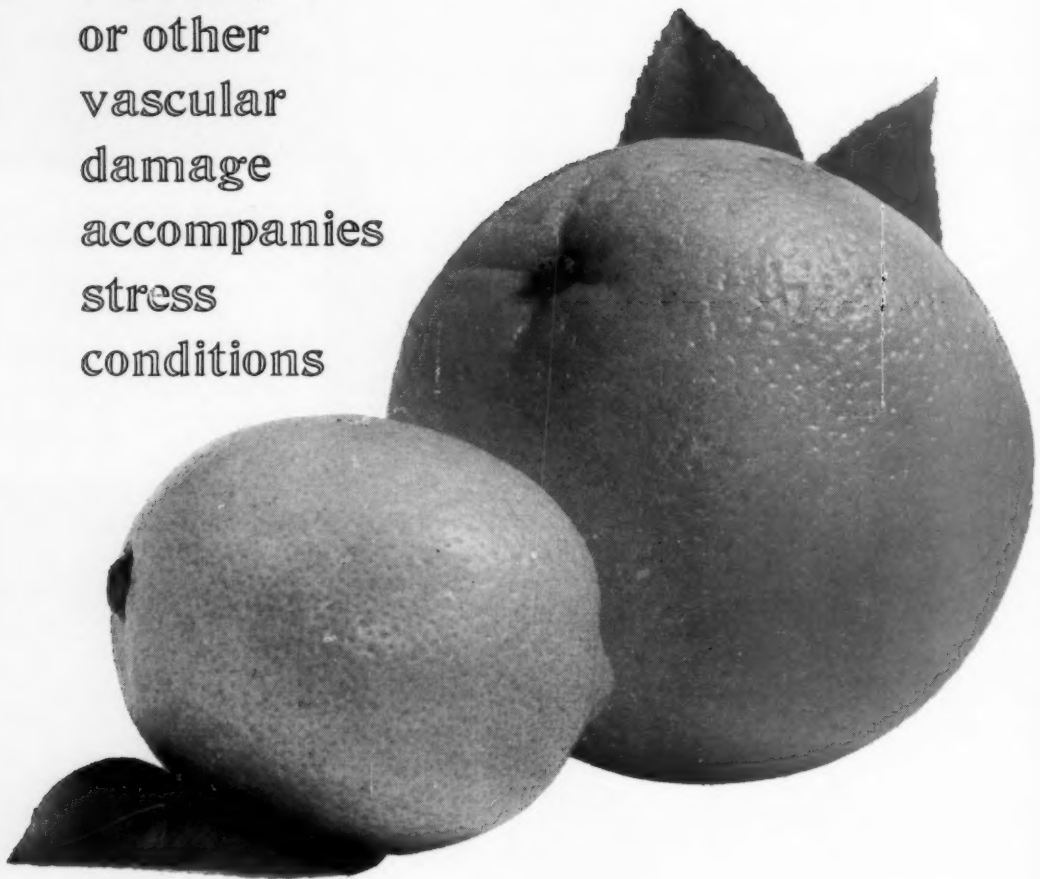


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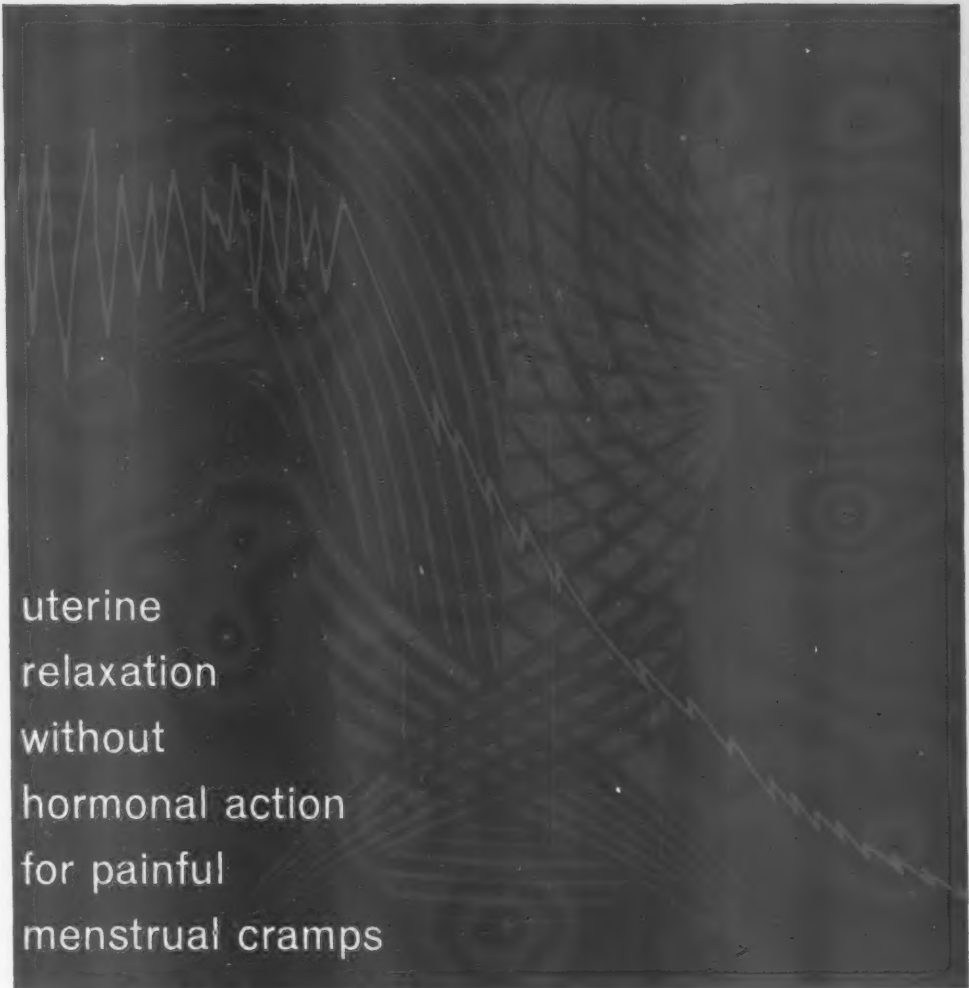
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**references:** (1) Voulgaris, D. M.: Dysmenorrhea—Treatment with Isoxsuprine, Obstetrics and  
Gynecology, to be published. (2) Krantz, K. E.: Detailed reports in Mead Johnson research files.



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1. Giorlando, S. W., and Brandt, M. L., Am. J. Obst. & Gynec. 76:666 (Sept.) 1958. 2. Weiner, H. H., Clin. Med. 5: 25 (Jan.) 1958.

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Vol. XXXII, Fasc. III

CONTENTS

November 1959

<i>Malamos, B. K., Daikos, G. K., Samara, V., and Koutras, D. A.:</i> The use of radioiodine for the diagnosis and treatment of thyroid diseases	311
<i>Luft, R., Ikko, D., Gemzell, C.-A., and Olivecrona, H.:</i> The effect of human growth hormone in hypophysectomized human diabetic subjects	330
<i>Ikko, D., Luft, R., and Gemzell, C.-A.:</i> The effect of human growth hormone in man	341
<i>Gans, E.:</i> The F. S. H.-content of serum of intact and of gonadectomized rats and of rats treated with sex hormones	362
<i>Gans, E.:</i> The F. S. H.-content of serum of intact and of gonadectomized rats and of rats treated with sex hormones	373
<i>Timonen, S. and Väänänen, P.:</i> Uterine myoma. Some hormone assays	384
<i>Berde, B. and Saameli, K.:</i> The action of the synthetic polypeptide valyl-oxytocin on the human uterus <i>in vitro</i> and <i>in vivo</i>	391
<i>Croes-Buth, S., Paesi, F. J. A., and de Jongh, S. E.:</i> Stimulation of ovarian follicles in hypophysectomized rats by low dosages of oestradiol benzoate	399
<i>Hökefelt, B., Luft, R., and Sekkenes, J.:</i> Intermittent oedema with periodic excessive production of hydrocortisone in a patient with a pituitary tumour	411
<i>Chappel, C. I., Rona, G., and Gaudry, R.:</i> The influence of adrenal cortical steroids on cardiac necrosis produced by isoproterenol	419
<i>Fotherby, K., Forrest, A. D., and Laverty, S. G.:</i> The effect of chlorpromazine on adreno-cortical function	425
<i>Hohlweg, W. and Laschet, U.:</i> Zur Frage der Cortison- und Corticotropin-Wirkung auf das Hypophysen-Nebennierenrinden-System	437
<i>Fromm, G. A., Fideleff, E., Ferreño, M., Najenson, H., and Funes, J. C.:</i> Parathyroid function in patients with peptic ulcer	448

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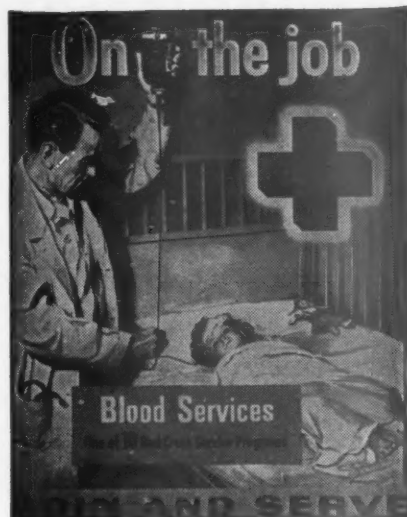
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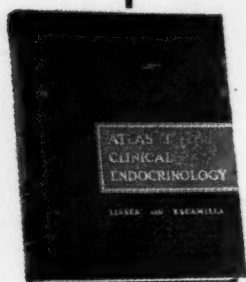


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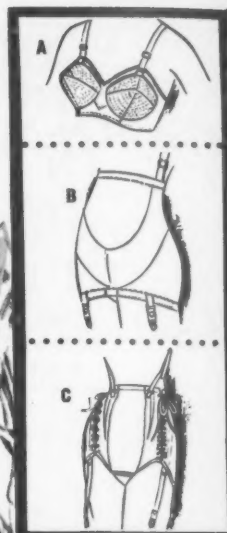
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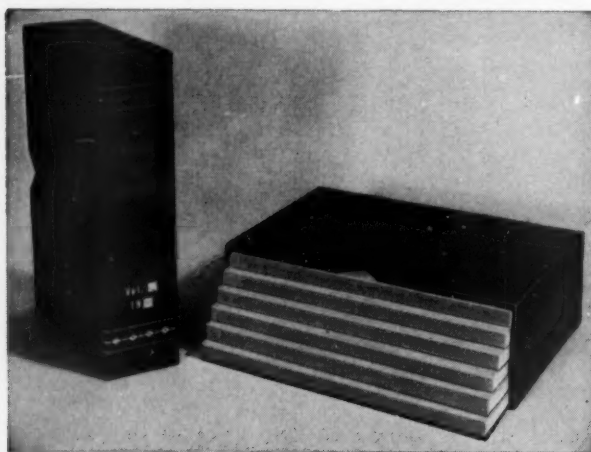
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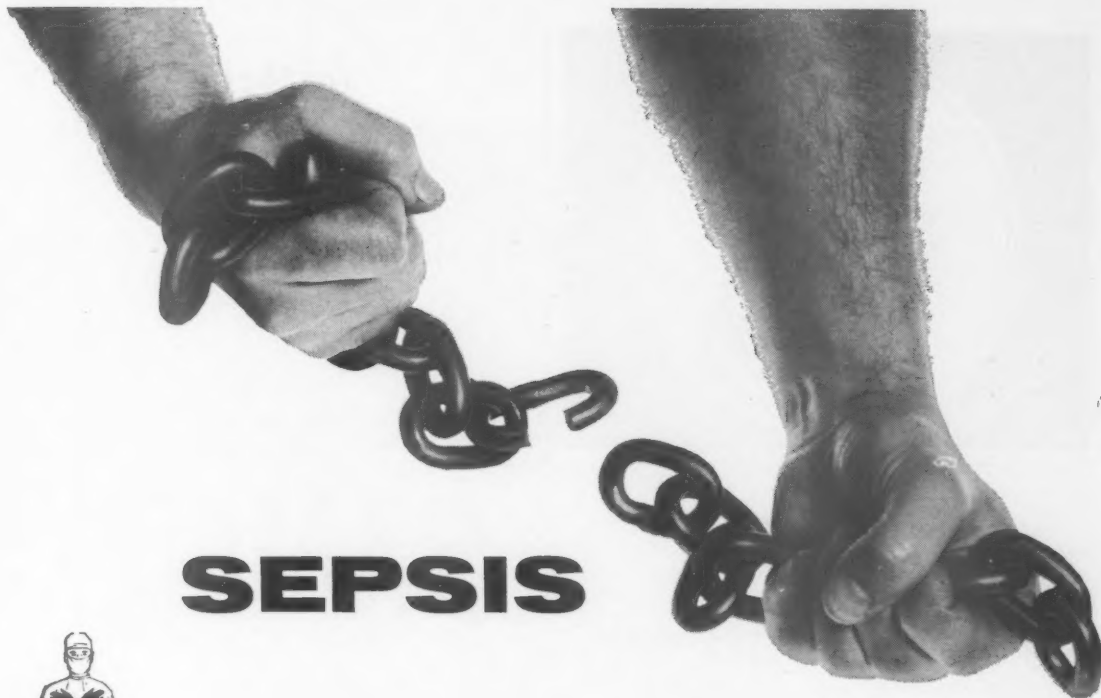
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1. Ausman, D. C.: J. Am.  
Geriatric Soc. 7:268, 1959.

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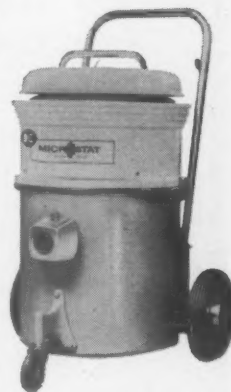
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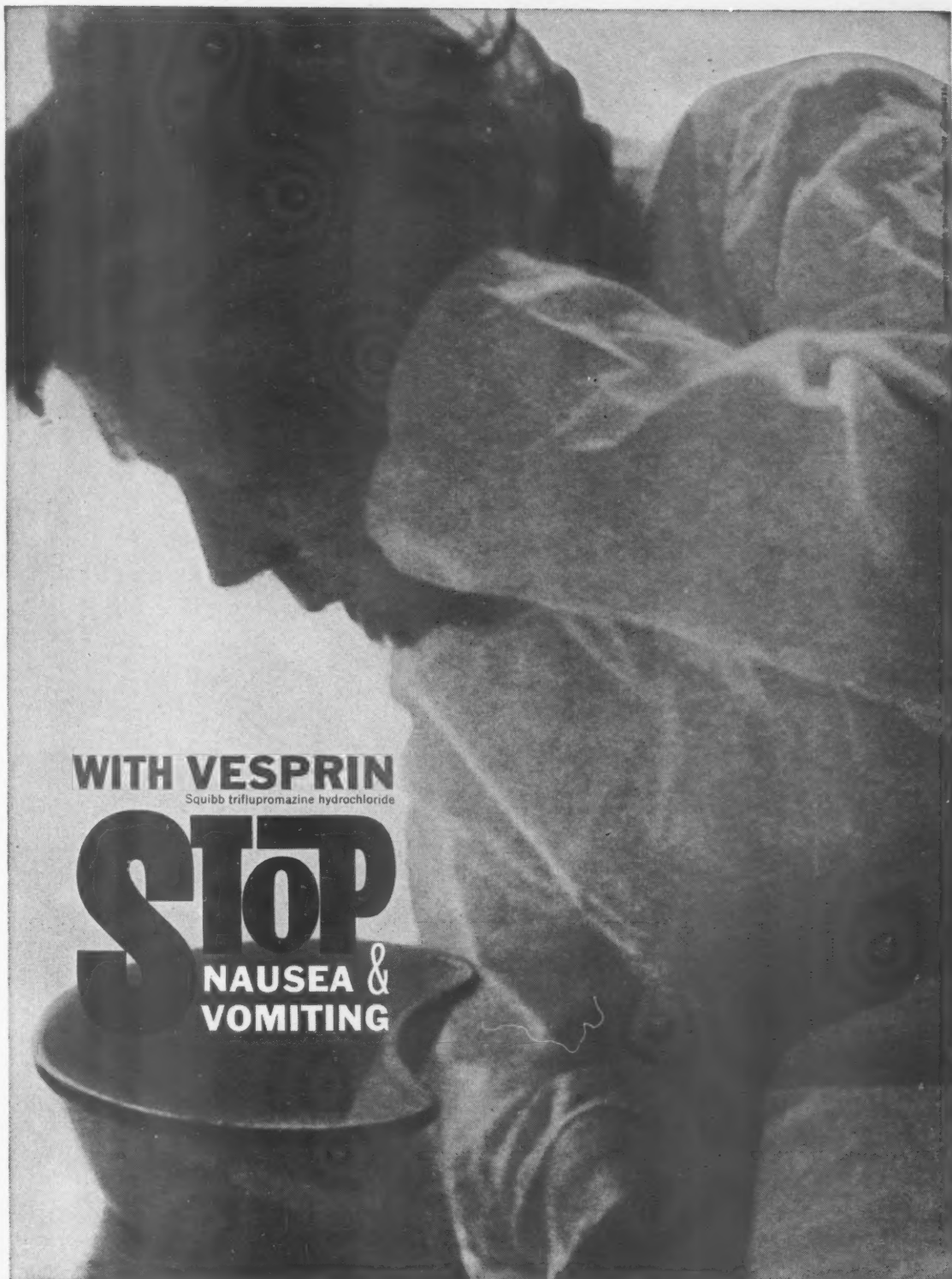
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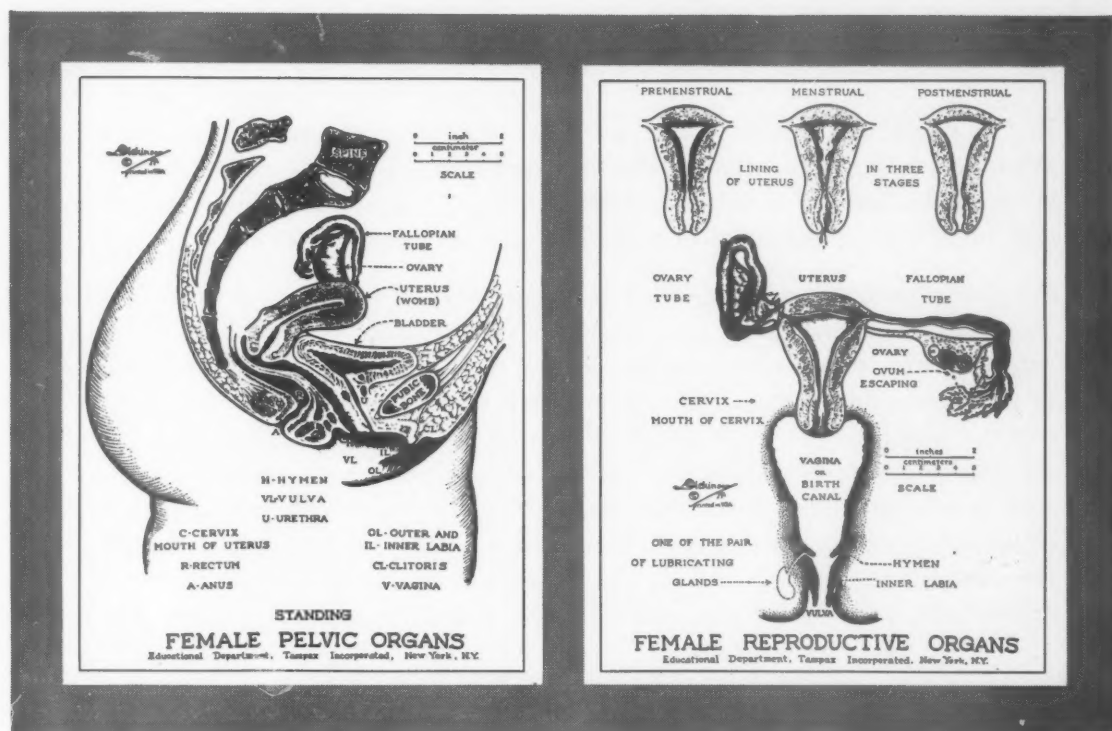
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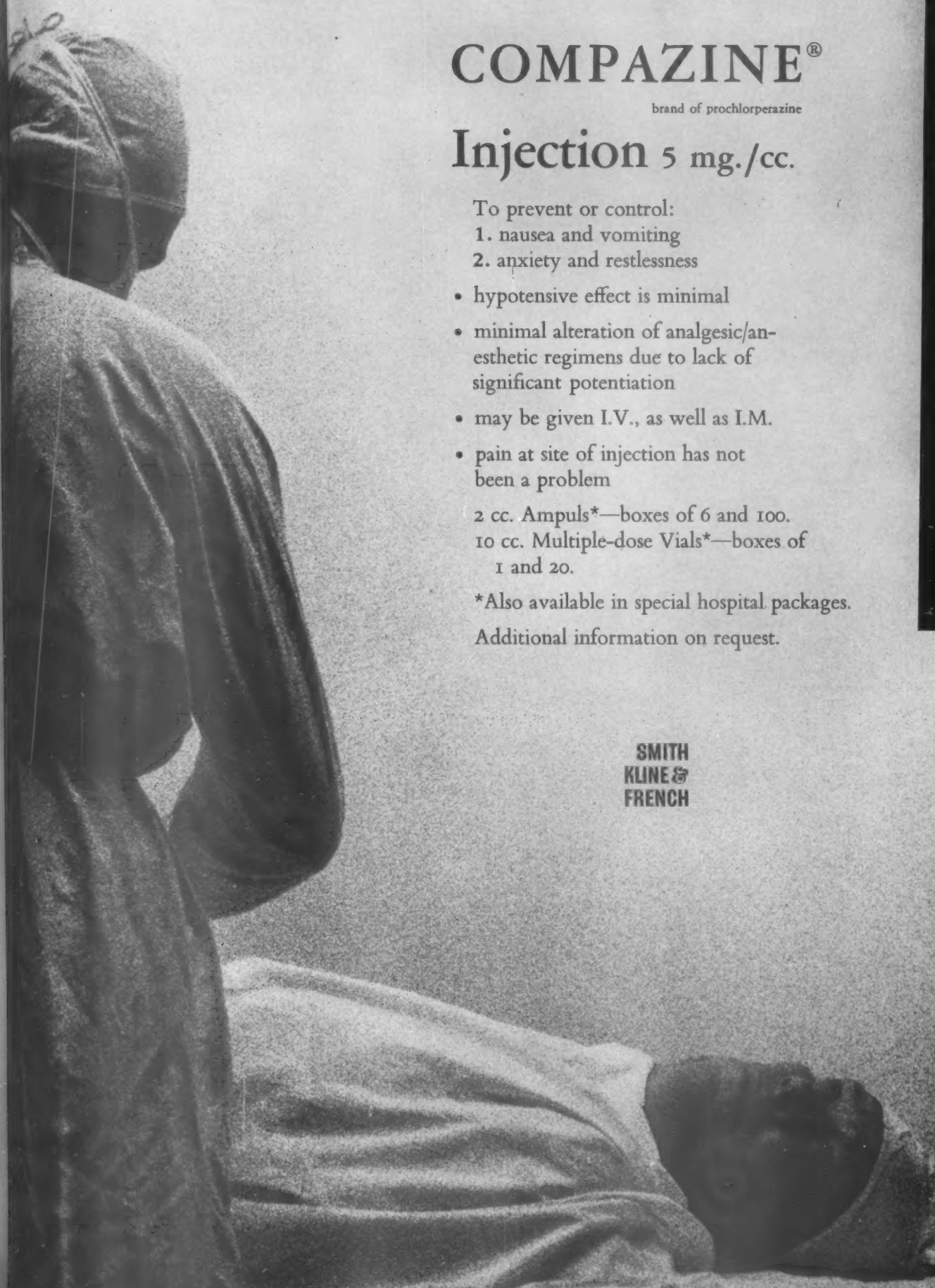
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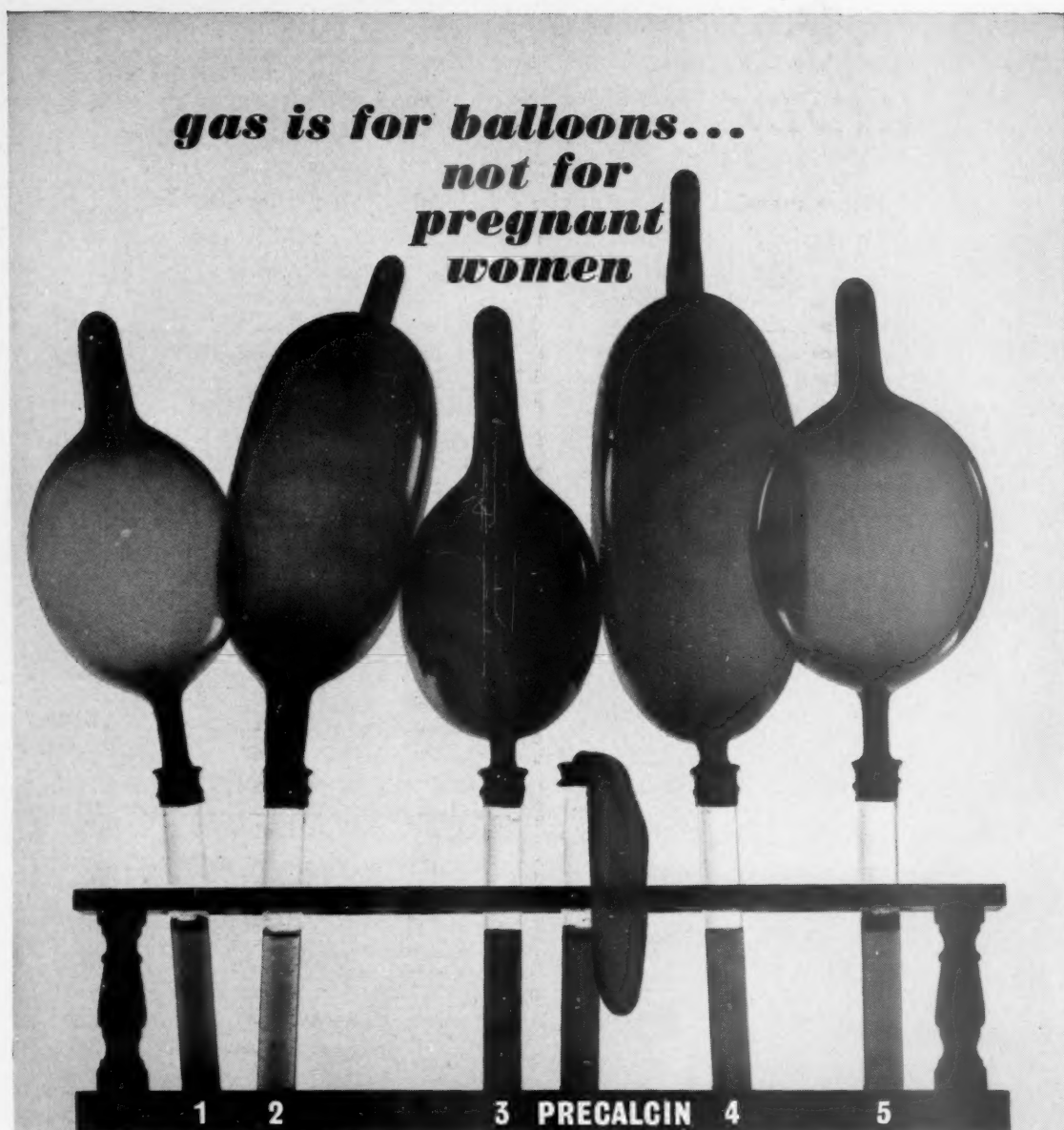
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Aeroplast Corporation -----	91		
American Ferment Co., Inc. -----	57	Parke, Davis & Company -----	42
American Sterilizer -----	90	Pet Milk Company -----	121
Amfre-Grant, Inc. -----	89	Pfizer Laboratories, Div. Chas. Pfizer & Co., Inc. -----	28, 29, 64
Armour Pharmaceutical Company ---	34, 59	Pitman-Moore Company -----	86
Arnar-Stone Laboratories, Inc. -----	97	Purdue Frederick Company, The -----	117
Ayerst Laboratories -----	16, 22, 47, 110		
Biochemical Procedures -----	124	Riker Laboratories -----	Third Cover
Breon & Co., George A. -----	76	Robins Co., Inc., A. H. -----	24
Burroughs Wellcome & Co. (U.S.A.) Inc. -----	46	Roche Laboratories, Div. of Hoffmann- La Roche Inc. -----	Second Cover
		Roche Laboratories, Div. of Hoffmann- La Roche Inc. -----	48, 49
Ciba Pharmaceutical Products --	58, 134, 135	Rorrig and Company, J. B. -----	41
		Rorer, Inc., William H. -----	115
Davis Company, F. A. -----	112	Ross Laboratories -----	113
Desitin Chemical Company -----	63		
Eaton Laboratories ---	19, 21, 52, 70, 71, 92	SchenLabs Pharmaceuticals, Inc. -----	78
Ethicon, Inc. -----	83, 84	Schmid, Inc., Julius -----	108
		Searle and Company, G. D. -----	9, 101
Fesler Company, Inc., The -----	66, 67	Smith Kline and French Laboratories -- -----	3, 43, 54, 62, 80, 81, 85, 136
Fuller Pharmaceutical Company -----	114	Squibb and Sons, E. R. -----	35, 36, 37, 125
		Strasenburgh Laboratories -----	75, 77, 79
Grafax Instrument Co. -----	133	Sunkist Growers -----	104, 105
Holland-Rantos Co., Inc. -----	40, 106		
Kent Company, Inc., The -----	123	Tailby-Nason Company, Inc. -----	55, 56
		Tampax Incorporated -----	129
Lederle Laboratories, a Div. of Ameri- can Cyanamid Company -----	32, 33, 50, 53, 114, 118, 124, 133	Teckla, White Cotton Gowns -----	120
Lilly and Company, Eli -----	100	Thomas, Publisher, Charles C -----	11
Lloyd Brothers, Inc. -----	118	Travenol Laboratories, Inc. -----	23
Massengill Company, The S. E. -----	17, 18, 93, 94	Walker Laboratories, Inc. -----	138
Mead Johnson Company -----	14, 98, 107	Wallace Laboratories -----	13, 30, 31, 51, 72, 88, 102, 111
Merck Sharp and Dohme -----	68, 69, 82	Warner-Chilcott Laboratories ----	7, 95, 119
Merck Sharp and Dohme ----	Fourth Cover	Westwood Pharmaceuticals -----	73, 74
Merrell Company, The Wm. S. -----	122	White Laboratories, Inc. -----	5, 26, 27
Mission Pharmacal Co. -----	133	Whittaker Laboratories, Inc. -----	124
		Williams & Wilkins Company -----	39
National Drug Company, The ----	20, 96, 99	Winthrop Laboratories -----	25
Nu-Lift, Division of Flexnit Corp. ----	118	Wyeth Laboratories --	60, 65, 103, 109, 132

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1. Wizenberg, M. J., et al.: Am. J. Obst. & Gynec. 78: 405 (Aug.) 1959.

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